CHAPTER 8

NEUROLOGICAL ASSESSMENT

INTRODUCTION

Background

The frequent association of subjective neurological symptoms subsequent to herbicide exposure has driven a great deal of the research into the potential neurotoxicity of dioxin. Studies of industrial accidents have demonstrated that the mixed sensorimotor neuropathy associated with extreme chlorophenol toxicity is reversible and there is no scientific evidence to date for any chronic central or peripheral neurological disease associated with low level 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure. Neurobehavioral endpoints in humans, the subject of intensive investigation in this and other studies of Vietnam veterans, are considered separately in Chapter 9, Psychological Assessment.

Earlier research (1, 2) into the effects of perinatal exposure to 2,4-D and 2,4,5-T on neurobehavioral function in weanling rats has been pursued in more recent studies from the same laboratory (3, 4). These and other studies in mice (5) and rabbits (6) have documented changes in the concentrations of several CNS neurotransmitters in association with 2,4-D-induced neurobehavioral dysfunction. In another series of experiments, the neurobehavioral effects of exposure to an ester of 2,4-D were found to be rapidly reversible and the authors proposed a cellular rather than biochemical basis for the tolerance that developed with repeated injections (7, 8, 9).

To date, there has been very little animal research into neurotoxic effects specific to TCDD. One report documented that the intracerebroventricular administration of TCDD in rats was far more toxic than the subcutaneous route, though specific neurological indices were not examined (10). Another study of endpoints associated with acute lethal doses of TCDD in rats concluded that the neuromuscular effects associated with the "wasting syndrome" were primarily on muscle tissue rather than peripheral nerves (11).

The early literature related to 2,4-D-induced neurotoxicity in humans has been summarized in the most recent report of the Air Force Health Study (AFHS) and will not be reviewed in detail here. In association with TCDD exposure, as with 2,4-D, a host of subjective neurological symptoms has been reported and grouped generically under the diagnosis of "neurasthenia." Numerous studies have been published describing populations exposed to TCDD by occupation (12-17), environmental contamination (18-22), and industrial accidents (23-29).

A recent report on the 1976 explosion in Seveso, Italy (24), described the results of examinations conducted in 1982 to 1983 and included objective data derived from a detailed neurological examination and electrophysiological testing. One hundred fifty-two subjects with chloracne, a reliable marker for high-level dioxin exposure, were compared with controls. An abnormality was detected in only 1 of 13 neurophysiological parameters and none of the exposed subjects was found to have a peripheral neuropathy by World Health Organization criteria. These findings were confirmed in another report as well (28). Similar results were

reported in a study conducted 30 years after a runaway reaction that occurred in a trichlorophenol plant in Nitro, West Virginia, in 1949 (15). By neurological examination and nerve conduction velocity studies, no differences were found in 204 exposed subjects (55% had chloracne) compared with 163 controls.

Point source environmental exposure to TCDD has been the focus of numerous epidemiologic studies some of which have included neurological indices in their protocols (18-22). In 1971, waste byproducts contaminated with TCDD from a chlorophenol manufacturing plant were mixed with oils and widely sprayed for dust control in residential areas of eastern Missouri near St. Louis. Soil concentrations in some areas reached 2,200 parts per billion. Comprehensive medical evaluations of exposed and unexposed cohorts have included detailed neurological examinations and in one report (21), quantitative studies of tactile, vibratory, and thermal sensations. A recent review article summarizes the results of these Missouri dioxin studies (30). To date there has been no clinical evidence for any central or peripheral neurological disease associated with these TCDD exposures. The first study (20) to report tissue levels of dioxin in relation to neurological findings found no correlation between the body burden of dioxin and abnormalities in the peripheral indices of pain and vibratory sensation and deep tendon reflexes.

Several studies of Vietnam veterans have included objective neurological data. In the Baseline examination of the AFHS (31), an increased incidence of abnormal Babinski reflexes was noted in Ranch Hand personnel relative to Comparisons, a finding that was not seen at the 1985 examination (32). In a study of 15 veterans who reported subjective symptoms in association with herbicide exposure, one subject was found to have a bilateral peripheral neuropathy related to alcohol abuse. In all others, nerve conduction velocity studies at five peripheral sites were normal (33).

One large-scale study (34) of American Legion veterans who served in Vietnam found an increased incidence of reported neurobehavioral disorders that suggested an association with herbicide exposure. However, the significance is limited by self-reporting bias, the lack of confirmation by clinical examination or medical record review, and the use of unvalidated exposure assumptions.

In contrast to the American Legion study, the Vietnam experience study conducted by the U.S. Centers for Disease Control (CDC) (35) compared 2,490 Vietnam veterans with 1,972 non-Vietnam veterans. Included in the study protocol were comprehensive neurological examinations, nerve conduction velocity studies, and neurophysiological indices of vibratory, thermal, and auditory sensation. Aside from an increased incidence of combat-related high-frequency hearing loss in a pattern typical of a noise etiology, no neurological abnormalities were noted in association with service in Southeast Asia (SEA).

In summary, animal research and studies of humans exposed to high levels of dioxin leave no doubt that the peripheral nervous system is a target organ for acute TCDD toxicity. Longitudinal studies would seem to indicate that the neurological signs and symptoms attributable to acute exposure resolve over time and are not associated with any long-term sequelae.

More detailed summaries of the pertinent scientific literature for the neurological assessment can be found in the report of the previous analyses of the 1987 examination data (36).

Summary of Previous Analyses of the 1987 Examination Data

The neurological health of the Ranch Hand group was not substantially different from the Comparison group. Of the six questionnaire variables relating to neurological disease, the only significant finding was that Ranch Hands had a higher incidence of hereditary and degenerative neurological disease, such as benign essential tremor. The statistical results of the group contrasts for 30 physical examination variables relating to cranial nerve function, peripheral nerve status, and CNS coordination processes were generally not significant. Unadjusted analyses disclosed marginally more balance/Romberg sign and coordination abnormalities for Ranch Hands than for Comparisons. Conversely, Ranch Hands had significantly fewer biceps reflex abnormalities than Comparisons. The adjusted analyses revealed a significant group-by-insecticide exposure interaction for the cranial nerve index (excluding neck range of motion). Stratified results showed a relative risk significantly greater than 1 for participants who had never been exposed to insecticides, and a relative risk marginally less than 1 for participants who had been exposed to insecticides. The adjusted analysis for coordination detected differences in the relative risks with occupation and insecticide exposure. Stratified analyses found a significant group difference for enlisted groundcrew who had never been exposed to insecticides. There were no significant differences for the other strata. Further investigation found a significant group difference for enlisted groundcrew after excluding the insecticide interaction, and a significant adjusted group difference overall after excluding both interactions. Ranch Hands had significantly more coordination abnormalities than Comparisons for each analysis. The longitudinal analyses for the cranial nerve index and the CNS index were not significant.

Parameters of the Neurological Assessment

Dependent Variables

The neurological assessment was primarily based on extensive physical examination data on cranial nerve function, peripheral nerve status, and CNS coordination processes. This information was supplemented by verified histories of neurological diseases.

Questionnaire Data

Data on all major health conditions since the date of the last health interview were collected during the 1987 health interview. All affirmative histories were subjected to medical records verification. The verified information was used to update the health status of each study participant. The neurological diseases and disorders were classified into eight International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) categories: inflammatory diseases (ICD codes 32000-32600), hereditary and degenerative diseases (ICD codes 33000-33700), peripheral disorders (ICD codes 35000-35900), disorders of the eye (ICD codes 37800-37956), external otitis (ICD codes 38010-38081), tympanic membrane disorder (ICD codes 38420-38500), hearing loss (ICD codes 38900-38999), and other neurological disorders (ICD codes 34000-34900). There were 389 cases in the ICD-9-CM category of other neurological disorders based on all assayed participants. The disorders in this category included multiple sclerosis (3 Ranch Hands and 1 Comparison), other demyelinating diseases of the central nervous system (2 Ranch Hands

and 1 Comparison), hemiplegia (4 Ranch Hands and 1 Comparison), other paralytic syndromes (9 Ranch Hands and 4 Comparisons), epilepsy (7 Ranch Hands and 1 Comparison), migraine (20 Ranch Hands and 14 Comparisons), catalepsy or narcolepsy (0 Ranch Hands and 1 Comparison), unspecified encephalopathy (157 Ranch Hands and 152 Comparisons), other conditions of the brain (1 Ranch Hand and 4 Comparisons), and other unspecified disorders of the nervous system (5 Ranch Hands and 2 Comparisons). Some participants had conditions in more than one category. The analyses of questionnaire information in the neurological assessment were based on verified data only. Each of the eight variables was coded as yes/no.

Participants with positive serological tests for syphilis and participants with a verified pre-SEA history of these disorders were excluded from all analyses of these neurological variables.

Physical Examination Data

During the physical examination, assessments were made of cranial nerve function, peripheral nerve status, and CNS coordination processes.

The evaluation of cranial nerve function was based on the following 17 variables: smell, visual fields, light reaction, ocular movement, facial sensation, corneal reflex, jaw clench, smile, palpebral fissure, balance, gag reflex, speech, tongue position relative to midline, palate and uvula movement, neck range of motion, cranial nerve index, and the index excluding neck range of motion. All of these variables were scored as normal/abnormal except jaw clench, which was scored as symmetric/deviated. Left and right determinations were combined to produce a single normal/abnormal result, where normal indicates that both left and right determinations were normal. The cranial nerve index was created by combining responses for the 15 cranial nerve parameters into a single index, which was classified as normal if all parameters were normal. An index was also created excluding the hypoglossal nerve (neck range of motion). No participants had an abnormal corneal reflex. No assayed participants had an abnormal jaw clench, gag reflex, or tongue position relative to midline. One assayed Comparison, but no Ranch Hands, had a palate and uvula movement abnormality.

Peripheral nerve status was assessed by light pin prick, light touch (cotton sticks), visual inspection of muscle mass (and palpation, if indicated), vibratory sensation as measured at the ankle with a tuning fork of 128 Hz, three deep tendon reflexes (patellar, Achilles, and biceps), and the Babinski reflex. Muscle status was a constructed variable using data on bulk, tone of upper and lower extremities and the strength of distal wrist extensors, ankle/toe flexors, proximal deltoids, and hip flexors. Muscle status was classified as normal if all of the components were normal. The reflexes were coded as normal if they were sluggish, active, or very active; reflexes classified as absent, transient clonus, or sustained clonus were coded as abnormal for the analyses.

The evaluation of CNS coordination processes was based on the analysis of the following variables: tremor, coordination, Romberg sign, gait, and CNS index. For these variables, multiple determinations were combined to form a single result, which was normal if all determinations were normal. Coordination was an index defined as normal if the Romberg

sign, finger-nose-finger and heel-knee-shin coordination processes, rapidly alternating movements of pronation/supination of hands, and rapid patting were normal. The CNS index was based on tremor, coordination, and gait; this index was coded as normal if all three of the components were normal.

Participants with positive serological tests for syphilis were excluded from all analyses of these neurological variables. Participants with contact lenses in place were excluded from the analysis of the corneal reflex (n=19 based on all participants). Participants with peripheral edema were excluded from the analyses of pin prick, light touch, and ankle vibration.

Covariates

The neurological assessment analyzed the effects of age, race, lifetime alcohol history, diabetic class, and insecticide exposure in the adjusted statistical analyses. Occupation was included as a covariate for the analyses of other neurological disorders because of a strong association. The lifetime alcohol history covariate was based on self-reported information from the questionnaire. The respondent's average daily alcohol consumption was determined for various drinking stages throughout his lifetime, and an estimate of the corresponding total number of drink-years (1 drink-year is the equivalent of drinking 1.5 ounces of 80-proof alcoholic beverage per day for 1 year) was derived. The exposure to insecticides covariate represents lifetime exposure based on self-reported questionnaire data.

Age and lifetime alcohol history were treated as continuous variables for all adjusted analyses, but they were categorized to explore interactions. Appendix Table G-1 presents the interaction summaries. Insecticide exposure was categorized (yes/no) for all analyses.

Relation to Baseline, 1985, and 1987 Studies

With the exception of the ICD-9-CM category of other neurological disorders, otitis, hearing loss, and the neurological summary indices, the variables analyzed for this study were also analyzed in the Baseline and 1985 studies. Other neurological disorders, the cranial nerve indices with and without neck range of motion, and the CNS index were variables added to the analysis of the 1985 examination. Analyses of otitis and hearing loss were included in the previous report of the 1987 examination.

The neurological longitudinal analyses were based on the cranial nerve index and the CNS index from the 1985 and 1987 neurological examinations conducted at the Scripps Clinic and Research Foundation (SCRF). To enhance the comparability, the longitudinal assessment contrasted differences between the 1985 and 1987 examinations.

Statistical Methods

The basic statistical analysis methods used in the neurological assessment are described in Chapter 4, Statistical Methods.

Table 8-1 summarizes the statistical analyses performed for the 1987 neurological assessment. The modeling strategy for the adjusted analyses was modified to always include age in the model, regardless of the statistical significance. In general, no covariates other than age were examined in the adjusted analyses of the questionnaire variables

TABLE 8-1.

Statistical Analysis for the Neurological Assessment

Dependent Variables

Variable	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Inflammatory Diseases	Q/PE-V	D	Yes No	--	U:LR,CS,FT
Hereditary and Degenerative Diseases	Q/PE-V	D	Yes No	AGE	U:LR A:LR
Peripheral Disorders	Q/PE-V	D	Yes No	AGE	U:LR A:LR
Disorders of the Eye	Q/PE-V	D	Yes No	AGE	U:LR A:LR
Otitis	Q/PE-V	D	Yes No	AGE	U:LR A:LR
Tympanic Membrane Disorders	Q/PE-V	D	Yes No	AGE	U:LR A:LR
Hearing Loss	Q/PE-V	D	Yes No	AGE	U:LR A:LR
Other Neurological Disorders	Q/PE-V	D	Yes No	AGE, OCC	U:LR A:LR
Smell	PE	D	Abnormal Normal	AGE	U:LR,CS,FT A:LR
Visual Fields	PE	D	Abnormal Normal	--	U:CS,FT
Light Reaction	PE	D	Abnormal Normal	AGE	U:LR,CS,FT A:LR
Ocular Movement	PE	D	Abnormal Normal	AGE	U:LR,CS,FT A:LR
Facial Sensation	PE	D	Abnormal Normal	AGE	U:LR,CS,FT A:LR
Corneal Reflex	PE	D	Abnormal Normal	--	--

TABLE 8-1. (Continued)

Statistical Analysis for the Neurological Assessment

Dependent Variables

Variable	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Jaw Clench	PE	D	Deviated Symmetric	--	--
Smile	PE	D	Abnormal Normal	AGE	U:LR A:LR
Palpebral Fissure	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR
Balance	PE	D	Abnormal Normal	--	U:LR,CS,FT
Gag Reflex	PE	D	Abnormal Normal	--	--
Speech	PE	D	Abnormal Normal	--	U:CS,FT
Tongue Position Relative to Midline	PE	D	Abnormal Normal	--	--
Palate and Uvula Movement	PE	D	Abnormal Normal	--	--
Neck Range of Motion	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR
Cranial Nerve Index	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR L:LR
Cranial Nerve Index Without Range of Motion	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR
Pin Prick	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR

TABLE 8-1. (Continued)

Statistical Analysis for the Neurological Assessment

Dependent Variables

Variable	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Light Touch	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR
Muscle Status	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR
Vibration	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR
Patellar Reflex	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR
Achilles Reflex	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR
Biceps Reflex	PE	D	Abnormal Normal	--	U:CS,FT
Babinski Reflex	PE	D	Abnormal Normal	--	U:LR,CS,FT
Tremor	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR
Coordination	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR
Romberg Sign	PE	D	Abnormal Normal	--	U:LR,CS,FT
Gait	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR

TABLE 8-1. (Continued)

Statistical Analysis for the Neurological Assessment

Dependent Variables

Variable	Data Source	Data Form	Cutpoints	Candidate Covariates	Statistical Analyses
Central Nervous System (CNS) Index	PE	D	Abnormal Normal	AGE,RACE, DRKYR,INS, DIAB	U:LR A:LR L:LR

Covariates

Variable (Abbreviation)	Data Source	Data Form	Cutpoints
Age (AGE)	MIL	D/C	Born ≥1942 Born <1942
Race (RACE)	MIL	D	Black Non-Black
Occupation (OCC)	MIL	D	Officer Enlisted Flyer Enlisted Groundcrew
Lifetime Alcohol History (DRKYR) (Drink-Years)	Q-SR	D/C	≤40 >40
Insecticide Exposure (INS)	Q-SR	D	Yes No
Diabetic Class (DIAB)	LAB/Q/PE-V	D	Diabetic: past history or ≥200 mg/dl glucose Impaired: ≥140-200 mg/dl glucose Normal: <140 mg/dl glucose

TABLE 8-1. (Continued)

Statistical Analysis for the Neurological Assessment

Abbreviations

Data Source:	LAB--1987 SCRF laboratory results MIL--Air Force military records PE--1987 SCRF physical examination Q-SR--NORC questionnaire (self-reported) Q/PE-V--1987 Questionnaire and physical examination (verified)
Data Form:	D--Discrete analysis only D/C--Appropriate form of analysis (either discrete or continuous)
Statistical Analyses:	U--Unadjusted analyses A--Adjusted analyses L--Longitudinal analyses
Statistical Methods:	CS--Chi-square contingency table test FT--Fisher's exact test LR--Logistic regression analysis

(occupation was also included for the analyses of other neurological disorders). The first part of this table lists the dependent variables analyzed, data source, data form, cutpoints, candidate covariates, and statistical analysis methods. The second part of this table provides a description of candidate covariates examined. Abbreviations are used extensively in the body of the table and are defined in the footnotes. Diabetes exhibited a significant positive association with dioxin (see Chapter 15, Endocrine Assessment). Consequently, clinical endpoints in the neurological assessment may be related to dioxin due to the association between dioxin and diabetes. To investigate this possibility, the dioxin effect was evaluated in the context of two models whenever diabetic class was retained in the final model. The results of the analysis adjusting for diabetic class are discussed and tabled in the body of the chapter. Appendix Table G-2 shows additional results for the final model excluding diabetic class. These followup analyses are only discussed if a meaningful change in the results occurred.

Some participants had missing dependent variable or covariate data. Consequently, these individuals could not be included in all analyses. Table 8-2 summarizes the number of participants with missing data, and the number who were excluded from analyses for medical reasons.

Appendix G-1 contains graphic displays of the neurological variables versus initial dioxin for the minimal and maximal cohorts, and the neurological variables versus current dioxin for Ranch Hands and Comparisons. Appendix G-2 presents graphics for dioxin-by-covariate interactions as determined by various statistical models. A guide to assist in interpreting the graphics is found in Chapter 4.

Three statistical models were used to examine the association between a neurological dependent variable and serum dioxin levels. One model related a dependent variable to each Ranch Hand's initial dioxin value (extrapolated from current dioxin values using a first-order pharmacokinetic model). A second model related a dependent variable to each Ranch Hand's current serum dioxin value and each Ranch Hand's time since tour. The phrase "time since tour" is often referred to as "time" in discussions of these results. Both of these models were implemented under the minimal and maximal assumptions (i.e., Ranch Hands with current dioxin above 10 ppt and above 5 ppt, respectively). The third model compared the neurological dependent variable for Ranch Hands having current dioxin values categorized as unknown, low, and high with Comparisons having background levels. The contrast of the entire Ranch Hand group with the complete Comparison group can be found in the previous report of analyses of the 1987 examination (36). All three models were implemented with and without covariate adjustment. Chapter 4 provides a more detailed discussion of the models.

TABLE 8-2.

Number of Participants Excluded and With Missing Data for the Neurological Assessment

Variable	Variable Use	Assumption (Ranch Hands Only) Minimal	Assumption (Ranch Hands Only) Maximal	Categorized Current Dioxin Ranch Hand	Categorized Current Dioxin Comparison
Visual Fields	DEP	0	0	0	2
Light Reaction	DEP	0	0	0	2
Ocular Movement	DEP	0	0	0	1
Facial Sensation	DEP	0	0	0	1
Corneal Reflex	DEP	7	8	7	6
Balance	DEP	0	0	0	1
Speech	DEP	0	0	0	1
Cranial Nerve Index	DEP	8	9	8	11
Cranial Nerve Index Without Range of Motion	DEP	8	9	8	11
Muscle Status	DEP	0	1	1	1
Patellar Reflex	DEP	0	0	0	1
Achilles Reflex	DEP	1	2	2	0
Coordination	DEP	0	1	1	1
Romberg Sign	DEP	0	0	0	1
Gait	DEP	0	1	1	1
CNS Index	DEP	0	1	1	1
Lifetime Alcohol History	COV	6	9	9	2
Diabetic Class	COV	2	2	3	2
Pre-SEA Inflammatory Diseases	EXC	0	0	0	5
Pre-SEA Hereditary and Degenerative Diseases	EXC	0	1	1	0
Pre-SEA Peripheral Disorders	EXC	0	1	2	3
Pre-SEA Disorders of the Eye	EXC	1	2	2	1
Pre-SEA Tympanic Membrane Disorder	EXC	5	5	6	5
Pre-SEA Otitis	EXC	0	0	0	1
Pre-SEA Hearing Loss	EXC	2	3	4	8
Pre-SEA Other Neurological Diseases	EXC	1	2	2	3
Syphilis	EXC	0	1	2	2
Pitting or Nonpitting Edema	EXC	9	12	10	14

DEP--Dependent variable (missing data).
COV--Covariate (missing data).
EXC--Exclusion.

RESULTS

Exposure Analysis

Questionnaire Variables

Inflammatory Diseases

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analyses of inflammatory diseases were not significant under both the minimal (Table 8-3 [a]: p=0.761) and maximal (Table 8-3 [b]: p=0.409) assumptions. Under both assumptions, there were only two cases of inflammatory disease. One was in the medium initial dioxin category, the other was in the high category. No adjusted analyses were done because of the sparse number of abnormalities.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The interaction between current dioxin and time since tour was not evaluated because only two Ranch Hands had a post-SEA history of inflammatory neurological disease. There was only one case within each time stratum.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The incidence of inflammatory diseases did not differ significantly among current dioxin categories in the unadjusted analysis (Table 8-3 [e]: p=0.616). No adjusted analysis was done because there were only three cases of inflammatory disease (one in each of the background, unknown, and high current dioxin categories, and none in the low category).

Hereditary and Degenerative Diseases

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, initial dioxin was not significantly associated with the incidence of hereditary and degenerative diseases (Table 8-4 [a-d]: p>0.55 for the unadjusted and adjusted analyses). The relative risk was less than 1 in each analysis.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The interaction between current dioxin and time since tour was not significant for the minimal and maximal analyses of hereditary and degenerative diseases (Table 8-4 [e-h]: p>0.45 for the unadjusted and adjusted analyses).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The incidence of hereditary and degenerative diseases did not differ significantly among the current dioxin categories in the unadjusted analysis (Table 8-4 [i]: 4.0%, 5.6%, 3.6%, and 3.2% for the background, unknown, low, and high current dioxin categories, p=0.524). The overall contrast was also not significant after adjusting for age (Table 8-4 [j]: p=0.612).

TABLE 8-3.

Analysis of Inflammatory Diseases

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.0	1.18 (0.41,3.43)	0.761
	Medium	260	0.4		
	High	131	0.8		
b) Maximal (n=741)	Low	184	0.0	1.46 (0.62,3.46)	0.409
	Medium	371	0.3		
	High	186	0.5		

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-3. (Continued)

Analysis of Inflammatory Diseases

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
c) Minimal						--
(n=521)	≤18.6	0.0 (72)	0.0 (128)	1.9 (54)	--	--
	>18.6	1.7 (58)	0.0 (132)	0.0 (77)	--	--
d) Maximal						--
(n=741)	≤18.6	0.0 (106)	0.0 (191)	1.2 (83)	--	--
	>18.6	0.0 (78)	0.6 (179)	0.0 (104)	--	--

--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-3. (Continued)

Analysis of Inflammatory Diseases

e) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	0.1	All Categories		0.616
Unknown	343	0.3	Unknown vs. Background	2.27 (0.14,36.48)	0.999
Low	196	0.0	Low vs. Background	--	0.999
High	187	0.5	High vs. Background	4.18 (0.26,67.18)	0.700
Total	1,505				

--: Relative risk, confidence interval, and p-value not given due to the absence of abnormalities.
Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-4.

Analysis of Hereditary and Degenerative Diseases

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	6.9	0.90 (0.62,1.31)	0.565
	Medium	260	3.1		
	High	131	3.8		
b) Maximal (n=740)	Low	183	4.4	0.94 (0.72,1.24)	0.684
	Medium	371	4.3		
	High	186	3.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	0.91 (0.62,1.33)	0.614	AGE (p=0.826)
d) Maximal (n=740)	0.96 (0.73,1.27)	0.781	AGE (p=0.517)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-4. (Continued)

Analysis of Hereditary and Degenerative Diseases

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.482[b]
(n=521)	≤18.6	6.9 (72)	3.9 (128)	3.7 (54)	0.81 (0.45,1.48)	0.495[c]
	>18.6	6.9 (58)	1.5 (132)	5.2 (77)	1.07 (0.66,1.73)	0.790[c]
f) Maximal						0.936[b]
(n=740)	≤18.6	2.9 (105)	5.8 (191)	2.4 (83)	0.98 (0.65,1.47)	0.907[c]
	>18.6	5.1 (78)	3.4 (179)	3.9 (104)	1.00 (0.69,1.45)	0.991[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.492[b]	AGE (p=0.727)
(n=521)	≤18.6	0.83 (0.45,1.54)	0.561[c]	
	>18.6	1.09 (0.66,1.78)	0.736[c]	
h) Maximal			0.943[b]	AGE (p=0.442)
(n=740)	≤18.6	1.01 (0.66,1.54)	0.972[c]	
	>18.6	1.03 (0.70,1.51)	0.887[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-4. (Continued)

Analysis of Hereditary and Degenerative Diseases

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	784	4.0	All Categories		0.524
Unknown	342	5.6	Unknown vs. Background	1.43 (0.80,2.57)	0.232
Low	196	3.6	Low vs. Background	0.90 (0.39,2.07)	0.804
High	187	3.2	High vs. Background	0.81 (0.33,1.96)	0.633
Total	1,509				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	784	All Categories		0.612	AGE (p=0.169)
Unknown	342	Unknown vs. Background	1.41 (0.78,2.53)	0.254	
Low	196	Low vs. Background	0.90 (0.39,2.09)	0.813	
High	187	High vs. Background	0.88 (0.36,2.16)	0.777	
Total	1,509				

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Peripheral Disorders

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In both the unadjusted and adjusted initial dioxin analyses, the relative risk of peripheral disorders was not significant under both the minimal and maximal assumptions (Table 8-5 [a-d]: $p>0.55$ for all analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin-by-time since tour interaction was not significant for either the minimal or maximal analyses of peripheral disorders (Table 8-5 [e-h]: $p>0.15$ in each unadjusted and adjusted analysis).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis of peripheral disorders was not significant, but the highest incidence of peripheral disorders was in the high current dioxin category (Table 8-5 [i]: 14.7%, 12.3%, 12.8%, and 16.0% for the background, unknown, low, and high current dioxin categories, $p>0.25$ for each contrast). The overall contrast, as well as the three Ranch Hand versus background contrasts, remained nonsignificant after adjustment for age (Table 8-5 [j]: $p>0.20$ for each contrast).

Disorders of the Eye

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, the initial dioxin analyses did not show a significant association with the incidence of eye disorders (Table 8-6 [a-d]: $p>0.35$ for the unadjusted and adjusted analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin and time since tour analyses of eye disorders did not find a significant interaction between current dioxin and time under both the minimal and maximal assumptions (Table 8-6 [e-h]: $p>0.80$ in each unadjusted and adjusted analysis).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The incidence of eye disorders did not differ significantly among the four current dioxin categories in the unadjusted analysis (Table 8-6 [i]: 15.8%, 16.7%, 16.9%, and 17.6% for the background, unknown, low, and high current dioxin categories, $p=0.930$). The overall contrast remained nonsignificant (Table 8-6 [j]: $p=0.801$) after adjustment for age.

Tympanic Membrane Disorders

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, initial dioxin was not significantly associated with the incidence of tympanic membrane disorders (Table 8-7 [a-d]: $p>0.60$ for the unadjusted and adjusted analyses).

TABLE 8-5.

Analysis of Peripheral Disorders

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	14.6	1.01 (0.83,1.24)	0.900
	Medium	260	14.2		
	High	131	13.7		
b) Maximal (n=740)	Low	183	14.8	1.00 (0.86,1.16)	0.999
	Medium	371	13.7		
	High	186	15.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.04 (0.85,1.28)	0.703	AGE (p=0.294)
d) Maximal (n=740)	1.05 (0.90,1.22)	0.564	AGE (p=0.003)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-5. (Continued)

Analysis of Peripheral Disorders

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.184[b]
(n=521)	≤18.6	12.5 (72)	16.4 (128)	7.4 (54)	0.82 (0.57,1.19)	0.302[c]
	>18.6	13.8 (58)	12.1 (132)	20.8 (77)	1.11 (0.86,1.44)	0.418[c]
f) Maximal						0.255[b]
(n=740)	≤18.6	15.1 (106)	13.6 (191)	13.3 (83)	0.89 (0.70,1.14)	0.371[c]
	>18.6	13.0 (77)	14.0 (179)	18.3 (104)	1.07 (0.88,1.31)	0.488[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.199[b]	AGE (p=0.363)
(n=521)	≤18.6	0.86 (0.59,1.25)	0.421[c]	
	>18.6	1.14 (0.88,1.49)	0.315[c]	
h) Maximal			0.263[b]	AGE (p=0.003)
(n=740)	≤18.6	0.96 (0.74,1.23)	0.732[c]	
	>18.6	1.15 (0.94,1.41)	0.186[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-5. (Continued)

Analysis of Peripheral Disorders

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	781	14.7	All Categories		0.564
Unknown	341	12.3	Unknown vs. Background	0.81 (0.56,1.19)	0.285
Low	196	12.8	Low vs. Background	0.85 (0.53,1.35)	0.482
High	187	16.0	High vs. Background	1.11 (0.71,1.71)	0.650
Total	1,505				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	781	All Categories		0.236	AGE (p<0.001)
Unknown	341	Unknown vs. Background	0.79 (0.54,1.16)	0.226	
Low	196	Low vs. Background	0.85 (0.53,1.36)	0.506	
High	187	High vs. Background	1.33 (0.85,2.08)	0.215	
Total	1,505				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-6.

Analysis of Disorders of the Eye

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=520)	Low	130	18.5	1.05 (0.87,1.26)	0.602
	Medium	259	17.4		
	High	131	18.3		
b) Maximal (n=739)	Low	183	15.3	1.05 (0.92,1.21)	0.475
	Medium	370	17.6		
	High	186	18.3		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=520)	1.07 (0.89,1.29)	0.486	AGE (p=0.419)
d) Maximal (n=739)	1.07 (0.93,1.23)	0.365	AGE (p=0.306)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-6. (Continued)

Analysis of Disorders of the Eye

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.920[b]
(n=520)	≤18.6	20.8 (72)	16.4 (128)	22.2 (54)	1.05 (0.79,1.41)	0.720[c]
	>18.6	15.5 (58)	18.3 (131)	15.6 (77)	1.08 (0.84,1.38)	0.563[c]
f) Maximal						0.832[b]
(n=739)	≤18.6	16.0 (106)	18.9 (191)	20.5 (83)	1.06 (0.87,1.31)	0.557[c]
	>18.6	13.0 (77)	17.4 (178)	15.4 (104)	1.10 (0.90,1.33)	0.346[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.956[b]	AGE (p=0.301)
(n=520)	≤18.6	1.10 (0.81,1.48)	0.546[c]	
	>18.6	1.11 (0.86,1.43)	0.423[c]	
h) Maximal			0.844[b]	AGE (p=0.165)
(n=739)	≤18.6	1.10 (0.89,1.36)	0.391[c]	
	>18.6	1.13 (0.93,1.37)	0.225[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-6. (Continued)

Analysis of Disorders of the Eye

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	15.8	All Categories		0.930
Unknown	342	16.7	Unknown vs. Background	1.06 (0.75,1.50)	0.727
Low	195	16.9	Low vs. Background	1.08 (0.71,1.65)	0.712
High	187	17.6	High vs. Background	1.14 (0.75,1.74)	0.546
Total	1,507				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	783	All Categories		0.801	AGE (p=0.011)
Unknown	342	Unknown vs. Background	1.05 (0.74,1.48)	0.798	
Low	195	Low vs. Background	1.09 (0.71,1.66)	0.699	
High	187	High vs. Background	1.24 (0.81,1.91)	0.321	
Total	1,507				

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-7.

Analysis of Tympanic Membrane Disorder

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=516)	Low	129	5.4	0.94 (0.68,1.29)	0.684
	Medium	257	5.8		
	High	130	6.2		
b) Maximal (n=736)	Low	184	3.8	1.01 (0.80,1.27)	0.959
	Medium	368	6.3		
	High	184	5.4		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=516)	0.99 (0.72,1.37)	0.950	AGE (p=0.153)
d) Maximal (n=736)	1.06 (0.84,1.35)	0.618	AGE (p=0.023)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-7. (Continued)

Analysis of Tympanic Membrane Disorder

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.435[b]
(n=516)	≤18.6	2.8 (72)	4.0 (125)	3.7 (54)	1.07 (0.58,1.97)	0.821[c]
	>18.6	8.6 (58)	8.4 (131)	6.6 (76)	0.80 (0.54,1.19)	0.270[c]
f) Maximal						0.844[b]
(n=736)	≤18.6	3.8 (106)	3.7 (189)	3.7 (82)	0.98 (0.63,1.51)	0.922[c]
	>18.6	6.4 (78)	8.4 (178)	5.8 (103)	0.93 (0.69,1.24)	0.616[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.419[b]	AGE (p=0.347)
(n=516)	≤18.6	1.14 (0.61,2.11)	0.681[c]	
	>18.6	0.84 (0.56,1.26)	0.406[c]	
h) Maximal			0.817[b]	AGE (p=0.066)
(n=736)	≤18.6	1.05 (0.67,1.65)	0.830[c]	
	>18.6	0.99 (0.73,1.33)	0.929[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-7. (Continued)

Analysis of Tympanic Membrane Disorder

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	779	4.1	All Categories		0.375
Unknown	342	3.5	Unknown vs. Background	0.85 (0.43,1.67)	0.635
Low	193	6.7	Low vs. Background	1.69 (0.87,3.28)	0.124
High	185	4.9	High vs. Background	1.19 (0.56,2.55)	0.647
Total	1,499				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	779	All Categories		0.315	AGE (p=0.087)
Unknown	342	Unknown vs. Background	0.83 (0.42,1.64)	0.600	
Low	193	Low vs. Background	1.70 (0.87,3.31)	0.116	
High	185	High vs. Background	1.33 (0.62,2.87)	0.470	
Total	1,499				

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The unadjusted and adjusted current dioxin and time since tour analyses of tympanic membrane disorders did not find a significant current dioxin-by-time interaction under either the minimal or maximal assumption (Table 8-7 [e-h]: $p>0.40$ in each analysis).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast was not significant in both the unadjusted and adjusted categorized current dioxin analysis of tympanic membrane disorders (Table 8-7 [i] and [j]: $p=0.375$ and $p=0.315$, respectively). The highest incidence was in the low current dioxin category (4.1%, 3.5%, 6.7%, and 4.9% for the background, unknown, low, and high current dioxin categories).

Otitis

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, the initial dioxin analyses did not find a significant risk of otitis (Table 8-8 [a-d]: $p>0.20$ for the unadjusted and adjusted analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal assumption, the unadjusted current dioxin and time since tour analysis of otitis did not show a significant current dioxin-by-time interaction (Table 8-8 [e]: $p=0.791$), but a significant interaction was found under the maximal assumption (Table 8-8 [f]: $p=0.032$). In the maximal cohort, the estimated relative risk of otitis was significantly less than 1 for Ranch Hands with a later tour (time$\leq$18.6: Est. RR=0.62, $p=0.012$). In this stratum, the incidence of otitis decreased with current levels of dioxin (14.2%, 7.3%, and 3.6% for the low, medium, and high current dioxin categories). The estimated relative risk was less than 1, but not significant, for Ranch Hands in the maximal cohort with an early tour (time>18.6: Est. RR=0.97, $p=0.760$).

Similar results were noted after adjusting for age. The current dioxin-by-time interaction was not significant under the minimal assumption (Table 8-8 [g]: $p=0.852$), and it remained significant under the maximal assumption (Table 8-8 [h]: $p=0.031$). The adjusted relative risk was significantly less than 1 for Ranch Hands with a later tour (time$\leq$18.6: Adj. RR=0.64, $p=0.020$).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The incidence of otitis did not differ significantly among the current dioxin categories in the unadjusted analysis (Table 8-8 [i]: 12.4%, 14.0%, 12.8%, and 8.6% for the background, unknown, low, and high current dioxin categories, $p=0.308$). The overall contrast remained nonsignificant after adjusting for age (Table 8-8 [j]: $p=0.633$).

Hearing Loss

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Neither the unadjusted minimal nor maximal analyses of hearing loss showed a significant association with initial dioxin (Table 8-9 [a] and [b]: $p=0.504$ for the minimal

TABLE 8-8.

Analysis of Otitis

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	8.5	1.04 (0.82,1.31)	0.761
	Medium	260	10.4		
	High	131	10.7		
b) Maximal (n=741)	Low	184	15.2	0.90 (0.76,1.08)	0.246
	Medium	371	10.8		
	High	186	8.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.13 (0.89,1.43)	0.331	AGE (p=0.004)
d) Maximal (n=741)	0.93 (0.78,1.12)	0.451	AGE (p=0.038)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-8. (Continued)

Analysis of Otitis

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.791[b]
(n=521)	≤18.6	2.8 (72)	7.0 (128)	3.7 (54)	0.86 (0.49,1.51)	0.601[c]
	>18.6	13.8 (58)	15.9 (132)	13.0 (77)	0.94 (0.71,1.23)	0.642[c]
f) Maximal						0.032[b]
(n=741)	≤18.6	14.2 (106)	7.3 (191)	3.6 (83)	0.62 (0.42,0.90)	0.012[c]
	>18.6	14.1 (78)	15.6 (179)	12.5 (104)	0.97 (0.79,1.19)	0.760[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.852[b]	AGE (p=0.032)
(n=521)	≤18.6	0.96 (0.54,1.69)	0.886[c]	
	>18.6	1.02 (0.76,1.35)	0.905[c]	
h) Maximal			0.031[b]	AGE (p=0.140)
(n=741)	≤18.6	0.64 (0.43,0.93)	0.020[c]	
	>18.6	1.00 (0.81,1.24)	0.973[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-8. (Continued)

Analysis of Otitis

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	12.4	All Categories		0.308
Unknown	343	14.0	Unknown vs. Background	1.15 (0.79,1.67)	0.459
Low	196	12.8	Low vs. Background	1.03 (0.65,1.66)	0.889
High	187	8.6	High vs. Background	0.66 (0.38,1.15)	0.145
Total	1,509				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	783	All Categories		0.633	AGE ($p<0.001$)
Unknown	343	Unknown vs. Background	1.13 (0.78,1.64)	0.532	
Low	196	Low vs. Background	1.04 (0.65,1.67)	0.863	
High	187	High vs. Background	0.76 (0.43,1.34)	0.343	
Total	1,509				

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-9.

Analysis of Hearing Loss

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=519)	Low	130	73.9	0.95 (0.81,1.11)	0.504
	Medium	259	71.4		
	High	130	70.0		
b) Maximal (n=738)	Low	183	73.8	0.94 (0.84,1.06)	0.344
	Medium	370	74.6		
	High	185	68.1		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=519)	1.16 (0.97,1.39)	0.100	AGE (p<0.001)
d) Maximal (n=738)	1.08 (0.95,1.22)	0.257	AGE (p<0.001)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-9. (Continued)

Analysis of Hearing Loss

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.555[b]
(n=519)	≤18.6	70.8 (72)	70.3 (128)	64.2 (53)	0.84 (0.66,1.08)	0.182[c]
	>18.6	79.3 (58)	72.5 (131)	72.7 (77)	0.93 (0.75,1.15)	0.517[c]
f) Maximal						0.674[b]
(n=738)	≤18.6	68.9 (106)	72.6 (190)	62.2 (82)	0.91 (0.77,1.09)	0.319[c]
	>18.6	84.6 (78)	76.4 (178)	70.2 (104)	0.87 (0.74,1.02)	0.095[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.748[b]	AGE (p<0.001)
(n=519)	≤18.6	1.14 (0.87,1.51)	0.347[c]	
	>18.6	1.21 (0.95,1.55)	0.125[c]	
h) Maximal			0.690[b]	AGE (p<0.001)
(n=738)	≤18.6	1.09 (0.91,1.32)	0.345[c]	
	>18.6	1.04 (0.87,1.24)	0.674[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-9. (Continued)

Analysis of Hearing Loss

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	776	76.0	All Categories		0.082
Unknown	341	75.1	Unknown vs. Background	0.95 (0.71,1.28)	0.731
Low	195	74.9	Low vs. Background	0.94 (0.65,1.35)	0.736
High	186	66.7	High vs. Background	0.63 (0.45,0.89)	0.009
Total	1,498				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	776	All Categories		0.660	AGE ($p<0.001$)
Unknown	341	Unknown vs. Background	0.82 (0.60,1.12)	0.211	
Low	195	Low vs. Background	0.95 (0.64,1.40)	0.787	
High	186	High vs. Background	0.91 (0.63,1.31)	0.600	
Total	1,498				

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

analysis and p=0.344 for the maximal analysis). After adjustment for age, the relative risk under the minimal assumption became marginally more than 1 (Table 8-9 [c]: Adj. RR=1.16, p=0.100), although the unadjusted incidence of hearing loss decreased with levels of initial dioxin (73.9%, 71.4%, and 70.0% for the low, medium, and high initial dioxin categories in the minimal cohort). Ranch Hands in the high initial dioxin category were on the average 4.8 years younger than those in the low category. The adjusted maximal analysis did not find a significant increased risk of hearing loss (Table 8-9 [d]: p=0.257).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the interaction between current dioxin and time since tour was not significant for the analyses of hearing loss (Table 8-9 [e-h]: p>0.55 in each of the unadjusted and adjusted analysis).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The incidence of hearing loss differed marginally among the current dioxin categories in the unadjusted analysis (Table 8-9 [i]: 76.0%, 75.1%, 74.9%, and 66.7% for the background, unknown, low, and high current dioxin categories, p=0.082). Relative to the background category, there was a significant decreased risk of hearing loss for Ranch Hands in the high current dioxin category (Est. RR=0.63, 95% C.I.: [0.45,0.89], p=0.009). However, this occurred because Ranch Hands in the high current dioxin category were on the average younger than Comparisons in the background category (63% of of Ranch Hands in the high category were born in or after 1942 versus 41% of Comparisons in the background category). For this reason, the overall contrast and the high versus background contrast became nonsignificant after adjustment for age (Table 8-9 [j]: p=0.660 and p=0.600, respectively).

Other Neurological Disorders

Preliminary screening analyses showed that occupation was highly associated with other neurological disorders. The incidence was much higher in enlisted flyers and enlisted groundcrew than in officers. This finding was independent of group membership. The percentages of Ranch Hands in the maximal cohort with other neurological disorders were 7.4 percent for officers, 32.6 percent for enlisted flyers, and 26.2 percent for enlisted groundcrew. For Comparisons with background levels of current dioxin, the incidences were 7.8 percent for officers, 33.6 percent for enlisted flyers, and 28.1 percent for enlisted groundcrew. Occupation is also highly associated with current levels of dioxin. Enlisted groundcrew have the highest current levels followed by enlisted flyers and officers (see Chapter 2, Dioxin Assay). Consequently, an additional model that included occupation was examined in each analysis. Appendix Table G-3 presents the results of these analyses.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted analyses did not find a significant association between initial dioxin and conditions in the other neurological disorders category under the minimal assumption (Table 8-10 [a]: p=0.392), but under the maximal assumption, the relative risk was significantly more than 1 (Table 8-10 [b]: Est. RR=1.24, p<0.001). The percentage of Ranch Hands in the maximal cohort with a post-SEA history of other neurological disorders increased with levels of initial dioxin (11.5%, 23.5%, and 25.8% for the low, medium, and high initial dioxin categories).

TABLE 8-10.

Analysis of Other Neurological Disorders

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Yes	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=520)	Low	130	16.2	1.07 (0.91,1.26)	0.392
	Medium	259	29.0		
	High	131	24.4		
b) Maximal (n=739)	Low	183	11.5	1.24 (1.09,1.40)	<0.001
	Medium	370	23.5		
	High	186	25.8		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=520)	1.20 (1.01,1.43)	0.037	AGE (p<0.001)
d) Maximal (n=739)	1.35 (1.18,1.54)	<0.001	AGE (p<0.001)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-10. (Continued)

Analysis of Other Neurological Disorders

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Yes/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.619[b]
(n=520)	≤18.6	16.7 (72)	28.4 (127)	18.5 (54)	1.11 (0.85,1.46)	0.437[c]
	>18.6	19.0 (58)	28.8 (132)	27.3 (77)	1.02 (0.82,1.26)	0.858[c]
f) Maximal						0.114[b]
(n=739)	≤18.6	7.6 (105)	21.1 (190)	25.3 (83)	1.37 (1.12,1.68)	0.002[c]
	>18.6	15.4 (78)	25.7 (179)	27.9 (104)	1.11 (0.94,1.31)	0.204[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.453[b]	AGE (p<0.001)
(n=520)	≤18.6	1.35 (1.01,1.79)	0.041[c]	
	>18.6	1.18 (0.94,1.47)	0.156[c]	
h) Maximal			0.082[b]	AGE (p<0.001)
(n=739)	≤18.6	1.58 (1.27,1.96)	<0.001[c]	
	>18.6	1.24 (1.05,1.48)	0.014[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-10. (Continued)

Analysis of Other Neurological Disorders

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Yes	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	781	21.6	All Categories		0.014
Unknown	342	17.0	Unknown vs. Background	0.74 (0.53,1.03)	0.073
Low	195	27.2	Low vs. Background	1.35 (0.94,1.93)	0.100
High	187	26.7	High vs. Background	1.32 (0.92,1.91)	0.135
Total	1,505				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	781	All Categories		<0.001	AGE (p<0.001)
Unknown	342	Unknown vs. Background	0.71 (0.50,0.99)	0.041	
Low	195	Low vs. Background	1.39 (0.96,2.01)	0.078	
High	187	High vs. Background	1.72 (1.17,2.51)	0.005	
Total	1,505				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Adjusting for age, the relative risk was significantly more than 1 under both the minimal (Table 8-10 [c]: Adj. RR=1.20, p=0.037) and maximal (Table 8-10 [d]: Adj. RR=1.35, p<0.001) assumptions. However, the relative risk became nonsignificant under both assumptions, after also including occupation in the model (Appendix Table G-3: Adj. RR=0.97, p=0.740 under the minimal assumption; Adj. RR=1.04, p=0.567 under the maximal assumption).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal assumption, the unadjusted current dioxin and time since tour analysis of the other neurological disorders category did not find a significant current dioxin-by-time interaction (Table 8-10 [e]: p=0.619). The interaction between current dioxin and time was also not significant under the maximal assumption (Table 8-10 [f]: p=0.114), but there was a significant association between current dioxin and other neurological disorders for Ranch Hands with a later tour (time≤18.6: Est. RR=1.37, p=0.002; % yes: 7.6%, 21.1%, and 25.3% for the low, medium, and high current dioxin categories).

After adjusting for age, the current dioxin-by-time interaction remained nonsignificant under the minimal assumption (Table 8-10 [g]: p=0.453), but the relative risk became significantly more than 1 for Ranch Hands with a later tour (time≤18.6: Adj. RR=1.35, p=0.041). Under the maximal assumption, the association between current dioxin and other neurological disorders differed marginally between time strata (Table 8-10 [h]: p=0.082) after adjusting for age. In each time stratum, the relative risk was significantly more than 1. The relative risk was 1.58 (p<0.001) for Ranch Hands in the maximal cohort with a later tour and 1.24 (p=0.014) for those with an earlier tour. However, adjusting for age and occupation, the current dioxin-by-time interaction and all within time stratum results were not significant under both assumptions (Appendix Table G-3: p>0.10 for all analyses).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The incidence of conditions in the other neurological disorders category differed significantly among current dioxin categories in the unadjusted analysis (Table 8-10 [i]: 21.6%, 17.0%, 27.2%, and 26.7% for the background, unknown, low, and high current dioxin categories, p=0.014). The relative risk for the unknown versus background contrast was marginally less than 1 (Est. RR=0.74, 95% C.I.: [0.53,1.03], p=0.073) and marginally more than 1 for the low versus background contrast (Est. RR=1.35, 95% C.I.: [0.94,1.93], p=0.100).

The overall contrast was highly significant after adjusting for age (Table 8-10 [j]: p<0.001). Each Ranch Hand versus background contrast was significant or marginally significant. There was a significant increased risk of other neurological disorders for the high current dioxin category (Adj. RR=1.72, 95% C.I.: [1.17,2.51], p=0.005) and a marginally significant increased risk in the low category (Adj. RR=1.39, 95% C.I.: [0.96,2.01], p=0.078). The relative risk was significantly less than 1 for the unknown category (Adj. RR=0.71, 95% C.I.: [0.50,0.99], p=0.041).

The results of the analyses adjusting for age and occupation were all nonsignificant (Appendix Table G-3: p>0.50 for each contrast). The relative risk for the unknown versus background contrast, which had been significantly less than 1, became more than 1 (Adj.

RR=1.12) and was larger than the relative risk for both the low versus background contrast (Adj. RR=1.09) and the high versus background contrast (Adj. RR=1.06).

Physical Examination Variables

Smell

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Both the minimal and maximal initial dioxin analyses of smell found a relative risk that was less than 1, but not significant (Table 8-11 [a-d]: $p>0.30$ for the unadjusted and adjusted analyses). There were only four Ranch Hands in the minimal cohort and five Ranch Hands in the maximal cohort with an abnormal sense of smell.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the current dioxin-by-time since tour interaction was not investigated because only one Ranch Hand with more than 18.6 years since tour had an abnormal sense of smell. The association between current dioxin and smell was not significant for Ranch Hands with 18.6 years or less since tour in the unadjusted analyses (Table 8-11 [e] and [f]: $p=0.375$ for the minimal analysis and $p=0.727$ for the maximal analysis). No adjusted analyses were done because there were so few abnormalities.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast was not significant in both the unadjusted and adjusted categorized current dioxin analyses of smell (Table 8-11 [g] and [h]: $p=0.227$ and $p=0.193$, respectively).

Visual Fields

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, there was only one Ranch Hand with a visual field abnormality. Table 8-12 [a] shows that he was in the low initial dioxin category under the minimal assumption. No analyses were performed because of the sparse number of abnormalities.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

No current dioxin and time since tour analyses were done because there was only one visual field abnormality.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The only two cases with an abnormal visual field were one Comparison in the background category and one Ranch Hand in the unknown current dioxin category. Neither the overall contrast (Table 8-12 [e]: $p=0.313$) nor the unknown versus background contrast

TABLE 8-11.

Analysis of Smell

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.8	0.61 (0.21,1.79)	0.324
	Medium	260	1.2		
	High	131	0.0		
b) Maximal (n=741)	Low	184	0.5	0.88 (0.44,1.75)	0.708
	Medium	371	0.8		
	High	186	0.5		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	0.67 (0.22,2.00)	0.432	AGE (p=0.421)
d) Maximal (n=741)	0.93 (0.45,1.89)	0.830	AGE (p=0.378)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-11. (Continued)

Analysis of Smell

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						--
(n=521)	≤18.6	1.4 (72)	1.6 (128)	0.0 (54)	0.50 (0.11,2.31)	0.375[b]
	>18.6	0.0 (58)	0.8 (132)	0.0 (77)	--	--
f) Maximal						--
(n=741)	≤18.6	0.9 (106)	1.6 (191)	0.0 (83)	0.86 (0.36,2.03)	0.727[b]
	>18.6	0.0 (78)	0.6 (179)	0.0 (104)	--	--

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-11. (Continued)

Analysis of Smell

g) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	784	0.8	All Categories		0.227
Unknown	343	0.3	Unknown vs. Background	0.38 (0.05,3.16)	0.640
Low	196	1.5	Low vs. Background	2.02 (0.50,8.13)	0.522
High	187	0.0	High vs. Background	--	0.552
Total	1,510				

h) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	784	All Categories		0.193	AGE (p=0.176)
Unknown	343	Unknown vs. Background	0.37 (0.04,3.09)	0.359	
Low	196	Low vs. Background	2.05 (0.51,8.28)	0.317	
High	187	High vs. Background	--	--	
Total	1,510				

--: Relative risk/confidence interval/p-value not given due to the absence of abnormalities.
Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-12.

Analysis of Visual Fields

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)	p-Value
a) Minimal (n=521)	Low	130	0.8	--	--
	Medium	260	0.0		
	High	131	0.0		
b) Maximal (n=741)	Low	184	0.0	--	--
	Medium	371	0.3		
	High	186	0.0		

--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-12. (Continued)

Analysis of Visual Fields

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
c) Minimal (n=521)	≤18.6	0.0 (72)	0.0 (128)	0.0 (54)	--	--
	>18.6	1.7 (58)	0.0 (132)	0.0 (77)	--	--
d) Maximal (n=741)	≤18.6	0.0 (106)	0.0 (191)	0.0 (83)	--	--
	>18.6	0.0 (78)	0.6 (179)	0.0 (104)	--	--

--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-12. (Continued)

Analysis of Visual Fields

e) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	782	0.8	All Categories		0.313
Unknown	343	0.3	Unknown vs. Background	0.38 (0.05,3.15)	0.636
Low	196	0.0	Low vs. Background	--	0.520
High	187	0.0	High vs. Background	--	0.550
Total	1,508				

--: Relative risk and confidence interval not given due to the absence of abnormalities.
Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

was significant (p=0.636) in the unadjusted analysis. No adjusted analysis was done due to sparse data.

Light Reaction

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Initial dioxin was not associated significantly with the prevalence of light reaction abnormalities under both the minimal and maximal assumptions (Table 8-13 [a-d]: p>0.30 for the unadjusted and adjusted analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The interaction between current dioxin and time since tour was not evaluated under the minimal assumption because only one Ranch Hand with an early tour had an abnormal light reaction. He was in the high current dioxin category. The unadjusted minimal analysis did not find a significant association between current dioxin and light reaction for Ranch Hands with a later tour (Table 8-13 [e]: p=0.943). The current dioxin-by-time interaction was not significant in the unadjusted maximal analysis of light reaction (Table 8-13 [f]: p=0.432). No adjusted analysis was done because of the sparse number of abnormalities.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of light reaction abnormalities did not differ significantly among the four current dioxin categories in the unadjusted analysis (Table 8-13 [g]: p=0.565). The overall contrast remained nonsignificant after adjustment for age (Table 8-13 [h]: p=0.287).

Ocular Movement

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions there were only three ocular movement abnormalities. For the minimal cohort, they were all in the medium initial dioxin category; for the maximal cohort, three were in the medium initial dioxin category and one was in the low category. The association with initial dioxin was not significant in either cohort (Table 8-14 [a-d]: p>0.90 for the unadjusted and adjusted analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The interaction between current dioxin and time since tour could not be analyzed because no Ranch Hands with a later tour had an abnormal ocular movement. The association between current dioxin and ocular movement was not significant for Ranch Hands with an early tour in the unadjusted analyses (Table 8-14 [e]: p=0.783 for the minimal analysis; Table 8-14 [f]: p=0.818 for the maximal analysis). Adjusted analyses were not done due to the sparseness of the data.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of abnormal ocular movement did not differ significantly among the current dioxin categories in either the unadjusted (Table 8-14 [g]: p=0.165) or adjusted (Table 8-14 [h]: p=0.170) analysis.

TABLE 8-13.

Analysis of Light Reaction

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.8	1.49 (0.67,3.30)	0.346
	Medium	260	0.0		
	High	131	1.5		
b) Maximal (n=741)	Low	184	1.6	0.98 (0.54,1.77)	0.950
	Medium	371	0.3		
	High	186	1.1		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.42 (0.61,3.29)	0.435	AGE (p=0.541)
d) Maximal (n=741)	0.99 (0.54,1.82)	0.990	AGE (p=0.815)

[a]Relative risk for a twofold increase in dioxin.
Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-13. (Continued)

Analysis of Light Reaction

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						- -
(n=521)	≤18.6	1.4 (72)	0.0 (128)	1.9 (54)	0.95 (0.25,3.64)	0.943[b]
	>18.6	0.0 (58)	0.0 (132)	1.3 (77)	- -	- -
f) Maximal						0.432[†]
(n=741)	≤18.6	1.9 (106)	0.5 (191)	1.2 (83)	0.83 (0.34,1.99)	0.671[b]
	>18.6	1.3 (78)	0.0 (179)	1.0 (104)	1.35 (0.57,3.17)	0.494[b]

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
[†]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-13. (Continued)

Analysis of Light Reaction

g) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	782	1.0	All Categories		0.565
Unknown	343	0.9	Unknown vs. Background	0.85 (0.23,3.24)	0.999
Low	196	0.0	Low vs. Background	--	0.332
High	187	1.1	High vs. Background	1.05 (0.22,4.97)	0.999
Total	1,508				

h) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	782	All Categories		0.287	AGE (p=0.309)
Unknown	343	Unknown vs. Background	0.84 (0.22,3.18)	0.794	
Low	196	Low vs. Background	--	--	
High	187	High vs. Background	1.20 (0.25,5.87)	0.819	
Total	1,508				

--: Relative risk, confidence interval, and p-value not given due to the absence of abnormalities.
Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-14.

Analysis of Ocular Movement

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.0	0.97 (0.37,2.53)	0.958
	Medium	260	1.2		
	High	131	0.0		
b) Maximal (n=741)	Low	184	0.5	1.02 (0.51,2.08)	0.944
	Medium	371	0.8		
	High	186	0.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.01 (0.38,2.68)	0.988	AGE (p=0.781)
d) Maximal (n=741)	1.00 (0.49,2.07)	0.988	AGE (p=0.779)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-14. (Continued)

Analysis of Ocular Movement

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						--
(n=521)	≤18.6	0.0 (72)	0.0 (128)	0.0 (54)	--	--
	>18.6	0.0 (58)	2.3 (132)	0.0 (77)	0.82 (0.20,3.41)	0.783[b]
f) Maximal						--
(n=741)	≤18.6	0.0 (106)	0.0 (191)	0.0 (83)	--	--
	>18.6	1.3 (78)	1.7 (179)	0.0 (104)	0.88 (0.31,2.52)	0.818[b]

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-14. (Continued)

Analysis of Ocular Movement

g) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	0.5	All Categories		0.165
Unknown	343	0.3	Unknown vs. Background	0.57 (0.06,5.11)	0.999
Low	196	1.5	Low vs. Background	3.03 (0.67,13.63)	0.296
High	187	0.0	High vs. Background	--	0.848
Total	1,509				

h) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	783	All Categories		0.170	AGE (p=0.455)
Unknown	343	Unknown vs. Background	0.59 (0.07,5.31)	0.636	
Low	196	Low vs. Background	3.01 (0.67,13.56)	0.150	
High	187	High vs. Background	--	--	
Total	1,509				

--: Relative risk/confidence interval/p-value not given due to the absence of abnormalities.
Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Facial Sensation

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, initial dioxin was not associated significantly with the prevalence of facial sensation abnormalities in either the unadjusted or adjusted analyses (Table 8-15 [a-d]: $p>0.60$ for all analyses). There were only three assayed Ranch Hands with an abnormal facial sensation.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The interaction between current dioxin and time since tour was not investigated because there was only one Ranch Hand with an early tour who had a facial sensation abnormality. Under both the minimal and maximal assumptions, current dioxin was not associated significantly with facial sensation for Ranch Hands with a later tour (Table 8-15 [e] and [f]: $p=0.454$ and $p=0.203$, in the unadjusted analyses, respectively). No adjusted analysis was done because of sparse data.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of facial sensation abnormalities did not differ significantly among the current dioxin categories in both the unadjusted and adjusted categorized current dioxin analyses (Table 8-15 [g] and [h]: $p=0.543$ and $p=0.313$, respectively).

Smile

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Initial dioxin was not significantly associated with the prevalence of smile abnormalities under both the minimal and maximal assumptions (Table 8-16 [a-d]: $p>0.10$ for the unadjusted and adjusted analyses). Only three Ranch Hands in the minimal cohort and five Ranch Hands in the maximal cohort had an abnormal smile.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin-by-time since tour interaction was not analyzed because only one Ranch Hand with a later tour had a smile abnormality. For Ranch Hands with an early tour, current dioxin was marginally associated with smile in the unadjusted minimal analysis (Table 8-16 [e]: Est. RR=2.53, $p=0.059$), but there was no significant association in the unadjusted maximal analysis (Table 8-16 [f]: $p=0.668$). For the minimal analysis, both Ranch Hands with a later tour who had a smile abnormality were in the high current dioxin category. No adjusted analyses were done because of sparse data.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The categorized current dioxin analyses of smile did not reveal a significant contrast in either the unadjusted or adjusted analysis (Table 8-16 [g] and [h]: $p>0.35$ for all contrasts).

TABLE 8-15.

Analysis of Facial Sensation

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.8	0.87 (0.31,2.40)	0.779
	Medium	260	0.4		
	High	131	0.8		
b) Maximal (n=741)	Low	184	0.0	1.21 (0.57,2.58)	0.628
	Medium	371	0.5		
	High	186	0.5		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	0.77 (0.26,2.25)	0.619	AGE (p=0.365)
d) Maximal (n=741)	1.12 (0.51,2.44)	0.776	AGE (p=0.394)

[a]Relative risk for a twofold increase in dioxin.
Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-15. (Continued)

Analysis of Facial Sensation

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						--
(n=521)	≤18.6	0.0 (72)	0.8 (128)	1.9 (54)	1.55 (0.49,4.88)	0.454[b]
	>18.6	1.7 (58)	0.0 (132)	0.0 (77)	--	--
f) Maximal						--
(n=741)	≤18.6	0.0 (106)	0.5 (191)	1.2 (83)	1.88 (0.71,4.97)	0.203[b]
	>18.6	0.0 (78)	0.6 (179)	0.0 (104)	--	--

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-15. (Continued)

Analysis of Facial Sensation

g) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	0.6	All Categories		0.543
Unknown	343	0.0	Unknown vs. Background	--	0.334
Low	196	0.5	Low vs. Background	0.80 (0.09,6.87)	0.999
High	187	0.5	High vs. Background	0.84 (0.10,7.20)	0.999
Total	1,509				

h) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	783	All Categories		0.313	AGE (p=0.809)
Unknown	343	Unknown vs. Background	--	--	
Low	196	Low vs. Background	0.80 (0.09,6.87)	0.836	
High	187	High vs. Background	0.80 (0.09,7.10)	0.842	
Total	1,509				

--: Relative risk/confidence interval/p-value not given due to the absence of abnormalities.
Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-16.

Analysis of Smile

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.0	1.87 (0.88,3.98)	0.124
	Medium	260	0.4		
	High	131	1.5		
b) Maximal (n=741)	Low	184	1.1	1.24 (0.69,2.21)	0.485
	Medium	371	0.3		
	High	186	1.1		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.88 (0.88,4.02)	0.124	AGE (p=0.889)
d) Maximal (n=741)	1.18 (0.65,2.15)	0.588	AGE (p=0.518)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-16. (Continued)

Analysis of Smile

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						--
(n=521)	≤18.6	0.0 (72)	0.8 (128)	0.0 (54)	--	--
	>18.6	0.0 (58)	0.0 (132)	2.6 (77)	2.53 (0.96,6.66)	0.059[b]
f) Maximal						--
(n=741)	≤18.6	0.0 (106)	0.5 (191)	0.0 (83)	--	--
	>18.6	2.6 (78)	0.0 (179)	1.9 (104)	1.15 (0.60,2.19)	0.668[b]

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-16. (Continued)

Analysis of Smile

g) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	784	1.2	All Categories		0.711
Unknown	343	0.6	Unknown vs. Background	0.51 (0.11,2.35)	0.384
Low	196	0.5	Low vs. Background	0.44 (0.06,3.51)	0.439
High	187	1.1	High vs. Background	0.93 (0.20,4.34)	0.927
Total	1,510				

h) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	784	All Categories		0.671	AGE (p=0.190)
Unknown	343	Unknown vs. Background	0.49 (0.11,2.30)	0.369	
Low	196	Low vs. Background	0.45 (0.06,3.55)	0.445	
High	187	High vs. Background	1.11 (0.23,5.30)	0.898	
Total	1,510				

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Palpebral Fissure

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, the initial dioxin analyses did not find a significant association with palpebral fissure (Table 8-17 [a-d]: $p>0.35$ in the unadjusted and adjusted analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The interaction between current dioxin and time since tour was not significant for the minimal and maximal analyses of palpebral fissure (Table 8-17 [e-h]: $p>0.20$ in the unadjusted and adjusted analyses).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The percentages of participants with an abnormal palpebral fissure did not differ significantly among the current dioxin categories in the unadjusted analysis (Table 8-17 [i]: 1.3%, 1.2%, 2.0%, and 1.6% for the background, unknown, low, and high current dioxin categories, $p=0.850$). After adjustment for age, the overall contrast remained nonsignificant (Table 8-17 [j]: $p=0.803$).

Balance

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, initial dioxin was not significantly associated with balance in the unadjusted analyses (Table 8-18 [a] and [b]: $p=0.871$ and $p=0.479$). No adjusted analyses were done because only two assayed Ranch Hands had an abnormal balance (one in the medium initial dioxin category and one in the high category under both assumptions).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin-by-time since tour interaction could not be evaluated because no Ranch Hands with a later tour had an abnormal balance. Under both the minimal and maximal assumptions, current dioxin was not significantly associated with balance in the unadjusted analyses for Ranch Hands with an early tour (Table 8-18 [c] and [d]: $p=0.921$ and $p=0.770$, respectively). No adjusted analyses were done because of sparse data.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis of balance did not show a significant overall contrast (Table 8-18 [e]: $p=0.117$). There were no abnormalities in the background or unknown current dioxin categories and there was one abnormality in both the low and high current dioxin categories.

TABLE 8-17.

Analysis of Palpebral Fissure

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.8	1.27 (0.76,2.14)	0.376
	Medium	260	1.5		
	High	131	2.3		
b) Maximal (n=741)	Low	184	1.6	1.13 (0.75,1.70)	0.564
	Medium	371	1.1		
	High	186	2.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=519)	1.22 (0.71,2.08)	0.483	AGE (p=0.582) DIAB*INS (p=0.040)
d) Maximal (n=741)	1.12 (0.74,1.71)	0.598	AGE (p=0.857)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-17. (Continued)

Analysis of Palpebral Fissure

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.552[b]
(n=521)	≤18.6	0.0 (72)	1.6 (128)	0.0 (54)	0.79 (0.18,3.43)	0.758[c]
	>18.6	1.7 (58)	1.5 (132)	3.9 (77)	1.25 (0.70,2.23)	0.451[c]
f) Maximal						0.228[b]
(n=741)	≤18.6	1.9 (106)	1.1 (191)	0.0 (83)	0.67 (0.25,1.81)	0.427[c]
	>18.6	1.3 (78)	1.7 (179)	2.9 (104)	1.26 (0.78,2.02)	0.347[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.453[b]	AGE (p=0.744)
(n=519)	≤18.6	0.74 (0.18,3.08)	0.681[c]	DIAB*INS (p=0.038)
	>18.6	1.27 (0.71,2.26)	0.423[c]	
h) Maximal			0.229[b]	AGE (p=0.700)
(n=741)	≤18.6	0.66 (0.24,1.76)	0.403[c]	
	>18.6	1.22 (0.75,2.00)	0.420[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-17. (Continued)

Analysis of Palpebral Fissure

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	784	1.3	All Categories		0.850
Unknown	343	1.2	Unknown vs. Background	0.91 (0.28,2.93)	0.879
Low	196	2.0	Low vs. Background	1.61 (0.50,5.20)	0.424
High	187	1.6	High vs. Background	1.26 (0.34,4.63)	0.726
Total	1,510				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	784	All Categories		0.803	AGE (p=0.211)
Unknown	343	Unknown vs. Background	0.90 (0.28,2.88)	0.853	
Low	196	Low vs. Background	1.63 (0.50,5.25)	0.416	
High	187	High vs. Background	1.45 (0.39,5.42)	0.584	
Total	1,510				

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-18.

Analysis of Balance

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.0	1.10 (0.36,3.30)	0.871
	Medium	260	0.4		
	High	131	0.8		
b) Maximal (n=741)	Low	184	0.0	1.39 (0.58,3.34)	0.479
	Medium	371	0.3		
	High	186	0.5		

[a]Relative risk for a twofold increase in dioxin.
Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-18. (Continued)

Analysis of Balance

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
c) Minimal (n=521)						--
	≤18.6	0.0 (72)	0.0 (128)	0.0 (54)	--	--
	>18.6	0.0 (58)	0.8 (132)	1.3 (77)	0.92 (0.18,4.70)	0.921[b]
d) Maximal (n=741)						--
	≤18.6	0.0 (106)	0.0 (191)	0.0 (83)	--	--
	>18.6	0.0 (78)	0.6 (179)	1.0 (104)	1.21 (0.34,4.24)	0.770[b]

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-18. (Continued)

Analysis of Balance

e) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	0.0	All Categories		0.117
Unknown	343	0.0	Unknown vs. Background	--	--
Low	196	0.5	Low vs. Background	--	0.400
High	187	0.5	High vs. Background	--	0.386
Total	1,509				

--: Relative risk/confidence interval/p-value not given due to the absence of abnormalities.
Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Speech

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

No initial dioxin analyses were done for speech because only one Ranch Hand had a speech abnormality under both the minimal and maximal assumptions. Table 8-19 shows that he was in the medium initial dioxin category.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

No current dioxin and time since tour analyses were done because there was only one speech abnormality.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

For the categorized current dioxin analyses, there was one speech abnormality in the background category and one in the low current dioxin category. Neither the overall contrast nor the low versus background contrast was significant in the unadjusted analysis (Table 8-19 [e]: p=0.421 and p=0.720, respectively). No adjusted analysis was done due to sparse data.

Neck Range of Motion

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analyses of neck range of motion did not find a significant association under both the minimal (Table 8-20 [a]: p=0.748) and maximal (Table 8-20 [b]: p=0.356) assumptions. The adjusted minimal analysis revealed two significant initial dioxin-by-covariate interactions—initial dioxin-by-race (Table 8-20 [c]: p=0.001) and initial dioxin-by-diabetic class (p=0.008). Separate analyses were done for Blacks and non-Blacks to explore the interactions. The analyses for Blacks found that only one Black Ranch Hand had an abnormal range of motion and he was in the low initial dioxin category.

The initial dioxin-by-diabetic class interaction was significant for non-Blacks. Further stratification by diabetic class showed a significant association between initial dioxin and range of motion for non-Black diabetics (Appendix Table G-1: Adj. RR=2.20, p=0.002; % abnormal: 7.7%, 17.2%, and 21.1% for the low, medium, and high initial dioxin categories). Initial dioxin was not associated significantly with range of motion for either diabetically impaired non-Blacks (Adj. RR=0.52, p=0.221) or for normal non-Blacks (Adj. RR=1.20, p=0.267). After excluding the initial dioxin-by-covariate interactions, the relative risk was marginally more than 1 in the adjusted minimal analysis (Table 8-20 [c]: Adj. RR=1.24, p=0.087).

The initial dioxin-by-diabetic class interaction was also significant in the adjusted maximal analysis (Table 8-20 [d]: p=0.004). Stratified findings were consistent with the results of the adjusted minimal analysis for non-Blacks. For diabetic Ranch Hands, initial dioxin was associated significantly with range of motion (Appendix Table G-1: Adj. RR=1.85, p=0.004; % abnormal: 10.0%, 12.2%, and 19.4% for the low, medium, and high initial dioxin categories), but the association was not significant for either diabetically impaired (Adj. RR=0.61, p=0.122) or normal Ranch Hands (Adj. RR=1.01, p=0.956). After excluding

TABLE 8-19.

Analysis of Speech

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)	p-Value
a) Minimal (n=521)	Low	130	0.0	--	--
	Medium	260	0.4		
	High	131	0.0		
b) Maximal (n=741)	Low	184	0.0	--	--
	Medium	371	0.3		
	High	186	0.0		

--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-19. (Continued)

Analysis of Speech

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
c) Minimal						--
(n=521)	≤18.6	0.0 (72)	0.0 (128)	0.0 (54)	--	--
	>18.6	0.0 (58)	0.8 (132)	0.0 (77)	--	--
d) Maximal						--
(n=741)	≤18.6	0.0 (106)	0.0 (191)	0.0 (83)	--	--
	>18.6	0.0 (78)	0.6 (179)	0.0 (104)	--	--

--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-19. (Continued)

Analysis of Speech

e) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	0.1	All Categories		0.421
Unknown	343	0.0	Unknown vs. Background	--	0.999
Low	196	0.5	Low vs. Background	4.01 (0.25,64.40)	0.720
High	187	0.0	High vs. Background	--	0.999
Total	1,509				

--: Relative risk and confidence interval not given due to the absence of abnormalities.
Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-20.

Analysis of Neck Range of Motion

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	9.2	1.04 (0.82,1.31)	0.748
	Medium	260	11.2		
	High	131	9.2		
b) Maximal (n=741)	Low	184	14.1	0.92 (0.78,1.10)	0.356
	Medium	371	11.3		
	High	186	8.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=519)	1.24 (0.97,1.59)***	0.087***	INIT*RACE (p=0.001) INIT*DIAB (p=0.008) AGE (p<0.001)
d) Maximal (n=739)	1.05 (0.87,1.27)***	0.597***	INIT*DIAB (p=0.004) AGE*RACE (p=0.003)

[a]Relative risk for a twofold increase in dioxin.

***Log_2 (initial dioxin)-by-covariate interaction ($p \leq 0.01$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.
INIT: Log_2 (initial dioxin).

TABLE 8-20. (Continued)

Analysis of Neck Range of Motion

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=521)						0.110[b]
	≤18.6	8.3 (72)	12.5 (128)	1.9 (54)	0.74 (0.47,1.18)	0.207[c]
	>18.6	6.9 (58)	12.1 (132)	13.0 (77)	1.14 (0.86,1.52)	0.359[c]
f) Maximal (n=741)						0.024[b]
	≤18.6	16.0 (106)	11.0 (191)	6.0 (83)	0.71 (0.52,0.96)	0.024[c]
	>18.6	11.5 (78)	11.2 (179)	11.5 (104)	1.08 (0.86,1.34)	0.516[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=521)			0.257[b]	AGE*RACE (p=0.003)
	≤18.6	1.06 (0.65,1.71)	0.824[c]	
	>18.6	1.45 (1.07,1.96)	0.017[c]	
h) Maximal (n=741)			0.026[b]	AGE*RACE (p=0.004)
	≤18.6	0.83 (0.59,1.16)	0.270[c]	
	>18.6	1.30 (1.03,1.65)	0.029[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-20. (Continued)

Analysis of Neck Range of Motion

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	784	11.7	All Categories		0.692
Unknown	343	12.2	Unknown vs. Background	1.05 (0.71,1.55)	0.808
Low	196	12.2	Low vs. Background	1.05 (0.65,1.69)	0.843
High	187	9.1	High vs. Background	0.75 (0.44,1.30)	0.305
Total	1,510				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	782	All Categories		0.830**	DXCAT*DIAB (p=0.039)
					AGE (p<0.001)
Unknown	342	Unknown vs. Background	0.97 (0.63,1.47)**	0.867**	RACE (p=0.004)
Low	194	Low vs. Background	1.11 (0.66,1.86)**	0.703**	DIAB*INS (p=0.025)
High	187	High vs. Background	1.28 (0.71,2.32)**	0.413**	
Total	1,505				

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.
DXCAT: Categorized current dioxin.

the interaction, the adjusted maximal analysis did not find a significant association (Table 8-20 [d]: p=0.597).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The unadjusted current dioxin and time since tour analyses of range of motion did not find a significant current dioxin-by-time interaction under the minimal assumption (Table 8-20 [e]: p=0.110), but under the maximal assumption, the interaction was significant (Table 8-20 [f]: p=0.024). The relative risk was significantly less than 1 for Ranch Hands in the maximal cohort with a later tour (time≤18.6: Est. RR=0.71, p=0.024; % abnormal: 16.0%, 11.0%, and 6.0% for the low, medium, and high current dioxin categories). The relative risk was more than 1, but not significant, for Ranch Hands in the maximal cohort with an early tour (time>18.6: Est. RR=1.08, p=0.516; % abnormal: 11.5%, 11.2%, and 11.5% for the low, medium, and high current dioxin categories).

In the adjusted minimal analysis, the current dioxin-by-time interaction remained nonsignificant (Table 8-20 [g]: p=0.257), but the relative risk for Ranch Hands with an early tour became significant (time>18.6: Adj. RR=1.45, p=0.017) after adjustment for the age-by-race interaction. The interaction between current dioxin and time remained significant in the adjusted maximal analysis (Table 8-20 [g]: p=0.026), but the significance of the within time strata results changed. After adjustment for the age-by-race interaction, the relative risk became nonsignificant for Ranch Hands with a later tour (time≤18.6: Adj. RR=0.83, p=0.270), and it became significantly more than 1 for Ranch Hands with an early tour (time>18.6: Adj. RR=1.30, p=0.029).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of range of motion abnormalities did not differ significantly among current dioxin categories in the unadjusted analysis (Table 8-20 [i]: 11.7%, 12.2%, 12.2%, and 9.1% for the background, unknown, low, and high current dioxin categories, p=0.692). The adjusted analysis found a significant interaction between categorized current dioxin and diabetic class (Table 8-20 [j]: p=0.039). Appendix Table G-1 presents stratified results that show a marginally significant difference among the percentages of abnormalities within the diabetic stratum (15.2%, 10.5%, 5.9%, and 22.6% for the background, unknown, low, and high current dioxin categories, p=0.094). However, none of the three Ranch Hand versus background contrasts was significant (p>0.10 for each contrast). The overall contrast was not significant in either the diabetically impaired stratum (p=0.240) or in the normal stratum (p=0.631). After excluding the interaction, the adjusted analysis was not significant (Table 8-20 [j]: p>0.40 for all contrasts).

Cranial Nerve Index

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analyses of the cranial nerve index were not significant under both the minimal (Table 8-21 [a]: p=0.812) and maximal (Table 8-21 [b]: p=0.467) assumptions. However, after adjustment for the age-by-race interaction, the relative risk became marginally more than 1 under the minimal assumption (Table 8-21 [c]: Adj. RR=1.21, p=0.090). The percentages of participants in the minimal cohort with an abnormal

TABLE 8-21.

Analysis of Cranial Nerve Index

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=513)	Low	128	12.5	1.03 (0.83,1.26)	0.812
	Medium	256	15.2		
	High	129	12.4		
b) Maximal (n=732)	Low	183	17.5	0.95 (0.81,1.10)	0.467
	Medium	367	15.0		
	High	182	11.5		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=513)	1.21 (0.97,1.50)	0.090	AGE*RACE (p=0.010)
d) Maximal (n=730)	1.05 (0.89,1.23)**	0.591**	INIT*DIAB (p=0.034) AGE*RACE (p=0.033)

[a]Relative risk for a twofold increase in dioxin.

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-21. (Continued)

Analysis of Cranial Nerve Index

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.114[b]
(n=513)	≤18.6	10.0 (70)	16.8 (125)	3.8 (53)	0.76 (0.51,1.14)	0.186[c]
	>18.6	12.1 (58)	16.0 (131)	17.1 (76)	1.11 (0.86,1.43)	0.424[c]
f) Maximal						0.021[b]
(n=732)	≤18.6	20.0 (105)	14.4 (187)	7.4 (81)	0.74 (0.57,0.97)	0.027[c]
	>18.6	14.1 (78)	15.6 (179)	14.7 (102)	1.09 (0.89,1.32)	0.411[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.225[b]	AGE*RACE (p=0.012)
(n=513)	≤18.6	1.00 (0.65,1.52)	0.986[c]	
	>18.6	1.34 (1.02,1.74)	0.033[c]	
h) Maximal			0.023[b]	AGE*RACE (p=0.029)
(n=732)	≤18.6	0.84 (0.63,1.12)	0.236[c]	
	>18.6	1.25 (1.02,1.54)	0.034[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-21. (Continued)

Analysis of Cranial Nerve Index

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	773	16.0	All Categories		0.338
Unknown	341	14.7	Unknown vs. Background	0.90 (0.63,1.28)	0.559
Low	194	17.5	Low vs. Background	1.11 (0.73,1.69)	0.617
High	183	11.5	High vs. Background	0.68 (0.41,1.11)	0.123
Total	1,491				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	773	All Categories		0.665	AGE (p<0.001) RACE (p=0.063)
Unknown	341	Unknown vs. Background	0.84 (0.58,1.22)	0.356	
Low	194	Low vs. Background	1.14 (0.73,1.77)	0.558	
High	183	High vs. Background	0.98 (0.58,1.64)	0.931	
Total	1,491				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

cranial nerve index were 12.5, 15.2, and 12.4 percent for the low, medium, and high initial dioxin categories.

The initial dioxin-by-diabetic class interaction was significant in the adjusted maximal analysis (Table 8-21 [d]: p=0.034). Stratified results parallel the findings for range of motion. Appendix Table G-1 shows that there was a significant increased risk of cranial nerve index abnormalities associated with initial dioxin for diabetic Ranch Hands (Adj. RR=1.69, p=0.009; % abnormal: 10.0%, 12.2%, and 22.6% for the low, medium, and high initial dioxin categories). The relative risk was not significant for both diabetically impaired (Adj. RR=0.89, p=0.603) and normal Ranch Hands (Adj. RR=0.99, p=0.916). After excluding the interaction the adjusted maximal analysis was not significant (Table 8-21 [d]: Adj. RR=1.05, p=0.591).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin and time since tour analyses for the cranial nerve index displayed findings similar to the corresponding analyses for range of motion. In the unadjusted analyses, the current dioxin-by-time interaction was not significant under the minimal assumption (Table 8-21 [e]: p=0.114), but it was significant under the maximal assumption (Table 8-21 [f]: p=0.021). There was a significant decreased risk of cranial nerve index abnormalities for Ranch Hands in the maximal cohort with a later tour (time>18.6: Est. RR=0.74, p=0.027; % abnormal: 20.0%, 14.4%, and 7.4% for the low, medium, and high current dioxin categories) that contrasted with a nonsignificant increased risk for Ranch Hands in the maximal cohort with an early tour (time≤18.6: Est. RR=1.09, p=0.411).

After adjusting for the age-by-race interaction, the relative risk became significantly more than 1 for Ranch Hands in the minimal cohort with an early tour (Table 8-21 [g]: Adj. RR=1.34, p=0.033), although the current dioxin-by-time interaction remained nonsignificant (p=0.225). In the adjusted maximal analysis, the current dioxin-by-time interaction remained significant (Table 8-21 [h]: p=0.023). As in the adjusted minimal analysis, the adjusted maximal analysis found a relative risk significantly more than 1 for Ranch Hands with an early tour (time>18.6: Adj. RR=1.25, p=0.034). After adjustment, the relative risk became nonsignificant for Ranch Hands in the maximal cohort with a later tour (time≤18.6: Adj. RR=0.84, p=0.236).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis did not find a significant difference in the prevalence of cranial nerve index abnormalities among the four categories (Table 8-21 [i]: 16.0%, 14.7%, 17.5%, and 11.5% for the background, unknown, low, and high current dioxin categories, p=0.338). The overall contrast remained nonsignificant (Table 8-21 [j]: p=0.665) after adjustment for age and race.

Cranial Nerve Index Without Range of Motion

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, the cranial nerve index without range of motion was not associated significantly with initial dioxin (Table 8-22 [a-d]: p>0.65 for all unadjusted and adjusted analyses).

TABLE 8-22.

Analysis of Cranial Nerve Index Without Range of Motion

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=513)	Low	128	3.9	1.05 (0.75,1.48)	0.760
	Medium	256	4.3		
	High	129	5.4		
b) Maximal (n=732)	Low	183	4.4	1.06 (0.82,1.37)	0.653
	Medium	367	3.8		
	High	182	5.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=513)	1.04 (0.73,1.48)	0.829	AGE (p=0.826) INS (p=0.085)
d) Maximal (n=732)	1.05 (0.81,1.37)	0.692	AGE (p=0.833)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-22. (Continued)

Analysis of Cranial Nerve Index Without Range of Motion

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.620[b]
(n=513)	≤18.6	2.9 (70)	4.0 (125)	3.8 (53)	0.89 (0.46,1.72)	0.725[c]
	>18.6	5.2 (58)	4.6 (131)	6.6 (76)	1.08 (0.72,1.63)	0.716[c]
f) Maximal						0.509[b]
(n=732)	≤18.6	4.8 (105)	3.7 (187)	2.5 (81)	0.93 (0.59,1.46)	0.750[c]
	>18.6	3.9 (78)	5.0 (179)	4.9 (102)	1.12 (0.81,1.55)	0.499[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.612[b]	AGE (p=0.978)
(n=513)	≤18.6	0.87 (0.44,1.71)	0.687[c]	INS (p=0.087)
	>18.6	1.06 (0.69,1.63)	0.783[c]	
h) Maximal			0.509[b]	AGE (p=0.736)
(n=732)	≤18.6	0.92 (0.58,1.44)	0.710[c]	
	>18.6	1.10 (0.79,1.54)	0.562[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-22. (Continued)

Analysis of Cranial Nerve Index Without Range of Motion

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	773	5.1	All Categories		0.320
Unknown	341	2.9	Unknown vs. Background	0.57 (0.28,1.15)	0.117
Low	194	5.7	Low vs. Background	1.13 (0.57,2.25)	0.725
High	183	3.8	High vs. Background	0.75 (0.33,1.70)	0.489
Total	1,491				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	773	All Categories		0.277**	DXCAT*INS (p=0.018) AGE (p=0.018)
Unknown	341	Unknown vs. Background	0.53 (0.26,1.09)**	0.084**	
Low	194	Low vs. Background	1.09 (0.54,2.19)**	0.807**	
High	183	High vs. Background	0.84 (0.36,1.93)**	0.674**	
Total	1,491				

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The association between current dioxin and the cranial nerve index without range of motion did not differ significantly between time since tour strata under both the minimal and maximal assumptions (Table 8-22 [e-h]: p>0.50 for each unadjusted and adjusted analysis).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of cranial nerve index abnormalities, excluding range of motion abnormalities, did not differ significantly among current dioxin categories in the unadjusted categorized current dioxin analysis (Table 8-22 [i]: 5.1%, 2.9%, 5.7%, and 3.8% for the background, unknown, low, and high current dioxin categories, p=0.320).

The adjusted analysis detected a significant categorized current dioxin-by-insecticide exposure interaction (Table 8-22 [j]: p=0.018). Stratified results showed a marginally significant overall contrast for participants who had never been exposed to insecticides (Appendix Table G-1: p=0.056). The percentages of abnormalities were 2.7, 2.0, 9.8, and 7.5 percent for the background, unknown, low, and high current dioxin categories in this stratum. Relative to the background category, there was a significant increased risk of an abnormality for Ranch Hands in the low current dioxin category (Adj. RR=3.76, 95% C.I.: [1.20,11.76], p=0.023) and a marginally significant increased risk for Ranch Hands in the high current dioxin category (Adj. RR=3.34, 95% C.I.: [0.98,11.34], p=0.053). The overall contrast was not significant for Ranch Hands who had been exposed to insecticides (p=0.113), although the adjusted relative risk was marginally less than 1 for the unknown versus background contrast (Adj. RR=0.46, 95% C.I.: [0.21,1.02], p=0.056). In this stratum, the prevalences for the background, unknown, low, and high current dioxin categories were 6.8, 3.3, 4.2, and 2.3 percent.

After excluding the interaction, the overall contrast was not significant in the adjusted analysis (Table 8-22 [j]: p=0.277), although there was a marginally significant decreased risk for Ranch Hands in the unknown category relative to the background category (Adj. RR=0.53, 95% C.I.: [0.26,1.09], p=0.084).

Pin Prick

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analyses did not find a significant association with pin prick under both the minimal (Table 8-23 [a]: p=0.941) and maximal (Table 8-23 [b]: p=0.632) assumptions. Under both assumptions, the adjusted analyses detected a significant initial dioxin-by-diabetic class interaction (Table 8-23 [c] and [d]: p=0.032 in the minimal analysis and p=0.042 in the maximal analysis). Stratified results under the minimal assumption showed a marginally significant increased risk of pin prick abnormalities for diabetic Ranch Hands (Appendix Table G-1: Adj. RR=1.58, p=0.069). In this stratum, the percentages of abnormalities were 7.7, 6.9, and 21.1 percent for the low, medium, and high initial dioxin categories. The relative risk was less than 1, but not significant in both the diabetically impaired (Adj. RR=0.20, p=0.175) and normal strata (Adj. RR=0.92, p=0.682). Stratified results under the maximal assumption showed that initial dioxin was marginally associated with a decreased risk of a pin prick abnormality for diabetically impaired Ranch Hands (Adj.

TABLE 8-23.

Analysis of Pin Prick

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=512)	Low	128	9.4	1.01 (0.76,1.34)	0.941
	Medium	255	5.9		
	High	129	6.2		
b) Maximal (n=729)	Low	183	6.0	1.05 (0.85,1.30)	0.632
	Medium	363	6.6		
	High	183	7.1		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=510)	1.07 (0.80,1.44)**	0.633**	INIT*DIAB (p=0.032) AGE*RACE (p=0.036)
d) Maximal (n=727)	1.10 (0.89,1.37)**	0.390**	INIT*DIAB (p=0.042) AGE*RACE (p=0.022)

[a]Relative risk for a twofold increase in dioxin.

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-23. (Continued)

Analysis of Pin Prick

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.123[b]
(n=512)	≤18.6	12.7 (71)	6.4 (125)	5.6 (54)	0.80 (0.50,1.29)	0.363[c]
	>18.6	7.0 (57)	3.9 (130)	8.0 (75)	1.28 (0.88,1.87)	0.194[c]
f) Maximal						0.971[b]
(n=729)	≤18.6	3.8 (105)	8.5 (189)	6.2 (81)	1.06 (0.77,1.45)	0.743[c]
	>18.6	7.7 (78)	5.8 (174)	6.9 (102)	1.06 (0.80,1.42)	0.676[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.184**[b]	CURR*TIME*DRKYR (p=0.019)
(n=506)	≤18.6	0.89 (0.55,1.46)**	0.649**[c]	AGE*RACE (p=0.039)
	>18.6	1.33 (0.91,1.95)**	0.137**[c]	
h) Maximal			0.970**[b]	CURR*TIME*DRKYR (p=0.029)
(n=720)	≤18.6	1.12 (0.80,1.57)**	0.500**[c]	AGE*RACE (p=0.030)
	>18.6	1.13 (0.84,1.52)**	0.406**[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.
CURR: Log_2 (current dioxin).
TIME: Time since tour.

TABLE 8-23. (Continued)

Analysis of Pin Prick

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	771	5.8	All Categories		0.925
Unknown	339	5.3	Unknown vs. Background	0.90 (0.52,1.59)	0.727
Low	194	5.2	Low vs. Background	0.88 (0.43,1.77)	0.714
High	183	6.6	High vs. Background	1.13 (0.59,2.19)	0.712
Total	1,487				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	769	All Categories		0.878	DIAB (p=0.010) AGE*INS (p=0.035)
Unknown	338	Unknown vs. Background	0.97 (0.54,1.71)	0.902	
Low	192	Low vs. Background	0.84 (0.40,1.77)	0.643	
High	183	High vs. Background	1.22 (0.61,2.42)	0.571	
Total	1,482				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

RR=0.44, p=0.093) that contrasted with nonsignificant increased risks for diabetic (Adj. RR=1.40, p=0.111) and normal (Adj. RR=1.06, p=0.678) Ranch Hands.

Under both assumptions, the adjusted initial dioxin analyses were not significant after excluding the interaction with diabetic class (Table 8-23 [c] and [d]: p=0.633 in the minimal analysis and p=0.390 in the maximal analysis).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

In the unadjusted analyses of pin prick, the interaction between current dioxin and time since tour was not significant under both the minimal (Table 8-23 [e]: p=0.123) and maximal (Table 8-23 [f]: p=0.971) assumptions. Under both assumptions, the adjusted analyses detected a significant current dioxin-by-time-by-lifetime alcohol history interaction (Table 8-23 [g] and [h]: p=0.019 in the minimal analysis and p=0.029 in the maximal analysis). Lifetime alcohol history was dichotomized to explore the interaction. Appendix Table G-1 shows that the current dioxin-by-time interaction was significant for Ranch Hands in the minimal cohort who had 40 drink-years or less (p=0.013). In this stratum, pin prick was associated significantly with current dioxin for Ranch Hands with an early tour ($\leq$40 drink-years, time>18.6: Adj. RR=1.81, p=0.011; % abnormal: 2.6%, 4.3%, and 10.7% for the low, medium, and high current dioxin categories). By contrast, the relative risk was less than 1, but not significant for Ranch Hands with a later tour ($\leq$40 drink-years, time$\leq$18.6: Adj. RR=0.73, p=0.337). The current dioxin-by-time interaction was not significant for Ranch Hands in the minimal cohort who had more than 40 drink-years (p=0.108).

Stratified results under the maximal assumption found that the interaction between current dioxin and time was not significant for Ranch Hands who had 40 drink-years or less (p=0.203), but it was significant for Ranch Hands who had more than 40 drink-years (p=0.022). In both lifetime alcohol history strata, current dioxin was marginally associated with pin prick for Ranch Hands with an early tour, but the direction of the results differed. The relative risk was marginally more than 1 for those who had 40 drink-years or less (Adj. RR=1.39, p=0.055; % abnormal: 6.3%, 4.1%, and 9.2% for the low, medium, and high current dioxin categories), while it was marginally less than 1 for those who had more than 40 drink-years (Adj. RR=0.42, p=0.089; % abnormal: 15.4%, 10.0%, and 0.0% for the low, medium, and high current dioxin categories). For Ranch Hands with a later tour, the relative risk was not significant in either lifetime alcohol history stratum.

After excluding the interaction with lifetime alcohol history, the adjusted analyses did not find a significant current dioxin-by-time interaction under both the minimal (Table 8-23 [g]: p=0.184) and maximal (Table 8-23 [h]: p=0.970) assumptions.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

Both the unadjusted and adjusted categorized current dioxin analyses of pin prick did not find a significant contrast (Table 8-23 [i] and [j]: p>0.55 for all contrasts).

Light Touch

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analyses did not find a significant association with light touch under both the minimal (Table 8-24 [a]: p=0.928) and maximal (Table 8-24 [b]: p=0.940) assumptions. The adjusted analyses were also not significant (Table 8-24 [c] and [d]: p=0.951 for the minimal analysis and p=0.938 for the maximal analysis).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal assumption, the association between current dioxin and light touch differed significantly between time since tour strata in the unadjusted analysis (Table 8-24 [e]: p=0.023), although the association was not significant within both time strata. The relative risk was more than 1 for Ranch Hands with an early tour (time>18.6: Est. RR=1.43, p=0.111) and it was less than 1 for Ranch Hands with a later tour (time≤18.6: Est. RR=0.59, p=0.129). The current dioxin-by-time interaction was not significant under the maximal assumption in the unadjusted analysis (Table 8-24 [f]: p=0.401).

The adjusted analyses supported the unadjusted findings. The interaction between current dioxin and time was significant under the minimal assumption (Table 8-24 [g]: p=0.048), although neither within time stratum result was significant (time>18.6: Adj. RR=1.39, p=0.182; time≤18.6: Adj. RR=0.62, p=0.207). Under the maximal assumption, the adjusted analysis did not find a significant current dioxin-by-time interaction (Table 8-24 [h]: p=0.397).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of light touch abnormalities did not differ significantly among current dioxin categories in the unadjusted analysis (Table 8-24 [i]: p=0.994). The adjusted analysis was also not significant (Table 8-24 [j]: p=0.989).

Muscle Status

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, the initial dioxin analyses of muscle status did not find a significant association (Table 8-25 [a-d]: p>0.35 for all unadjusted and adjusted analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The association between current dioxin and muscle status did not differ significantly between time since tour strata in the unadjusted analyses (Table 8-25 [e] and [f]: p=0.869 for the minimal analysis and p=0.629 for the maximal analysis). The current dioxin-by-time interaction remained nonsignificant after covariate adjustment (Table 8-25 [g] and [h]: p=0.710 for the minimal analysis and p=0.422 for the maximal analysis).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis did not find a significant difference in the prevalence of muscle status abnormalities among the four categories (Table 8-25 [i]: p=0.974). The adjusted analysis detected a significant categorized current dioxin-by-diabetic

TABLE 8-24.

Analysis of Light Touch

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=512)	Low	128	6.3	0.99 (0.69,1.40)	0.928
	Medium	255	3.9		
	High	129	3.9		
b) Maximal (n=729)	Low	183	4.4	1.01 (0.78,1.30)	0.940
	Medium	363	4.7		
	High	183	4.4		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=504)	1.01 (0.69,1.50)	0.951	DIAB (p=0.039) AGE*RACE (p=0.017) AGE*DRKYR (p=0.043)
d) Maximal (n=727)	0.99 (0.75,1.30)	0.938	DIAB (p=0.116) AGE*RACE (p=0.019)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-24. (Continued)

Analysis of Light Touch

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.023[b]
(n=512)	≤18.6	8.5 (71)	4.8 (125)	1.9 (54)	0.59 (0.30,1.17)	0.129[c]
	>18.6	3.5 (57)	3.1 (130)	5.3 (75)	1.43 (0.92,2.22)	0.111[c]
f) Maximal						0.401[b]
(n=729)	≤18.6	2.9 (105)	6.4 (189)	2.5 (81)	0.89 (0.59,1.35)	0.583[c]
	>18.6	5.1 (78)	4.0 (174)	4.9 (102)	1.12 (0.80,1.56)	0.517[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.048[b]	DIAB (p=0.060)
(n=504)	≤18.6	0.62 (0.30,1.30)	0.207[c]	AGE*RACE (p=0.029)
	>18.6	1.39 (0.86,2.24)	0.182[c]	AGE*DRKYR (p=0.035)
h) Maximal			0.397[b]	DIAB (p=0.135)
(n=727)	≤18.6	0.85 (0.54,1.36)	0.504[c]	AGE*RACE (p=0.020)
	>18.6	1.08 (0.77,1.53)	0.648[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-24. (Continued)

Analysis of Light Touch

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	771	4.3	All Categories		0.994
Unknown	339	4.1	Unknown vs. Background	0.96 (0.51,1.82)	0.909
Low	194	4.1	Low vs. Background	0.96 (0.44,2.12)	0.923
High	183	3.8	High vs. Background	0.89 (0.39,2.04)	0.783
Total	1,487				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	769	All Categories		0.989	AGE (p=0.377) DIAB*INS (p=0.044)
Unknown	338	Unknown vs. Background	1.09 (0.57,2.09)	0.797	
Low	192	Low vs. Background	0.97 (0.42,2.27)	0.943	
High	183	High vs. Background	0.93 (0.39,2.22)	0.876	
Total	1,482				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-25.

Analysis of Muscle Status

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.8	1.03 (0.61,1.71)	0.922
	Medium	260	2.3		
	High	131	2.3		
b) Maximal (n=740)	Low	183	1.1	1.17 (0.79,1.72)	0.439
	Medium	371	1.9		
	High	186	1.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=519)	1.09 (0.65,1.83)	0.747	AGE (p=0.175) DIAB (p=0.126)
d) Maximal (n=729)	1.21 (0.80,1.83)	0.381	AGE (p=0.064) DIAB*DRKYR (p=0.005)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-25. (Continued)

Analysis of Muscle Status

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=521)						0.869[b]
	≤18.6	0.0 (72)	3.9 (128)	1.9 (54)	1.07 (0.51,2.25)	0.859[c]
	>18.6	3.5 (58)	0.0 (132)	2.6 (77)	0.98 (0.44,2.15)	0.953[c]
f) Maximal (n=740)						0.629[b]
	≤18.6	1.0 (105)	2.1 (191)	2.4 (83)	1.30 (0.75,2.25)	0.348[c]
	>18.6	1.3 (78)	1.1 (179)	1.9 (104)	1.07 (0.59,1.94)	0.835[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=519)			0.710[b]	AGE (p=0.127)
	≤18.6	1.28 (0.59,2.79)	0.533[c]	DIAB (p=0.141)
	>18.6	1.05 (0.48,2.31)	0.908[c]	
h) Maximal (n=729)			0.422[b]	AGE (p=0.041)
	≤18.6	1.55 (0.83,2.90)	0.167[c]	DIAB*DRKYR (p=0.005)
	>18.6	1.10 (0.59,2.03)	0.766[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-25. (Continued)

Analysis of Muscle Status

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	2.2	All Categories		0.974
Unknown	342	1.8	Unknown vs. Background	0.80 (0.31,2.06)	0.650
Low	196	2.0	Low vs. Background	0.94 (0.31,2.82)	0.910
High	187	2.1	High vs. Background	0.98 (0.33,2.96)	0.978
Total	1,508				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	779	All Categories		0.945**	DXCAT*DIAB (p=0.019) AGE (p=0.014)
Unknown	338	Unknown vs. Background	0.77 (0.30,1.99)**	0.586**	DIAB*DRKYR (p=0.011)
Low	192	Low vs. Background	0.92 (0.30,2.81)**	0.884**	
High	183	High vs. Background	1.08 (0.34,3.45)**	0.893**	
Total	1,492				

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

class interaction (Table 8-25 [j]: p=0.019). Stratified results did not reveal a significant contrast for either diabetic (Appendix Table G-1: p>0.30 for all contrasts) or normal participants (p>0.20 for all contrasts). The percentages of muscle status abnormalities differed significantly among categories for diabetically impaired participants (0.0%, 6.4%, 0.0%, and 0.0% for the background, unknown, low, and high current dioxin categories, p=0.022), but this finding was affected by the sparse number of abnormalities (three in the unknown category and none in the other categories). The interaction occurred partly because the high and background categories contained the highest percentage of abnormalities in the normal strata, the unknown category had the most abnormalities in the impaired strata, and the low current dioxin category had the highest percentage of abnormalities in the diabetic stratum.

After excluding the interaction, the adjusted analysis was not significant (Table 8-25 [j]: p>0.55 for all contrasts).

Vibration

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions the initial dioxin analyses did not find a significant association with vibration (Table 8-26 [a-d]: p>0.60 for all unadjusted and adjusted analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin-by-time since tour interaction was not significant in the analyses of vibration under both the minimal and maximal assumptions (Table 8-26 [e-h]: p>0.80 in each unadjusted and adjusted analysis).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of vibration abnormalities did not differ significantly among the current dioxin categories in the unadjusted analysis (Table 8-26 [i]: 1.4%, 0.9%, 1.6%, and 1.6% for the background, unknown, low, and high current dioxin categories, p=0.844). The overall contrast remained nonsignificant after covariate adjustment (Table 8-26 [j]: p=0.584).

Patellar Reflex

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analyses of the patellar reflex were not significant under both the minimal (Table 8-27 [a]: p=0.661) and maximal (Table 8-27 [b]: p=0.304) assumptions. The adjusted analyses were also not significant (Table 8-27 [c] and [d]: p=0.686 for the minimal analysis and p=0.182 for the maximal analysis).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the association between current dioxin and patellar reflex did not differ significantly between time since tour strata (Table 8-27 [e-h]: p>0.50 in each analysis).

TABLE 8-26.

Analysis of Vibration

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=512)	Low	128	2.3	0.87 (0.50,1.52)	0.620
	Medium	255	2.4		
	High	129	0.8		
b) Maximal (n=729)	Low	183	1.1	1.07 (0.72,1.60)	0.737
	Medium	363	1.9		
	High	183	1.6		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=512)	0.87 (0.48,1.59)	0.644	AGE*INS (p=0.005)
d) Maximal (n=729)	1.11 (0.73,1.70)	0.619	AGE*INS (p=0.005)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-26. (Continued)

Analysis of Vibration

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.847[b]
(n=512)	≤18.6	1.4 (71)	1.6 (125)	0.0 (54)	0.87 (0.28,2.72)	0.806[c]
	>18.6	5.3 (57)	2.3 (130)	1.3 (75)	0.76 (0.38,1.53)	0.438[c]
f) Maximal						0.885[b]
(n=729)	≤18.6	1.0 (105)	1.1 (189)	1.2 (81)	1.06 (0.49,2.30)	0.879[c]
	>18.6	1.3 (78)	2.9 (174)	2.0 (102)	0.99 (0.61,1.63)	0.974[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.897[b]	AGE*INS (p=0.004)
(n=512)	≤18.6	0.82 (0.25,2.71)	0.751[c]	
	>18.6	0.75 (0.36,1.59)	0.457[c]	
h) Maximal			0.900[b]	AGE*INS (p=0.006)
(n=727)	≤18.6	1.11 (0.50,2.48)	0.794[c]	DIAB (p=0.131)
	>18.6	1.05 (0.62,1.77)	0.862[c]	

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-26. (Continued)

Analysis of Vibration

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	771	1.4	All Categories		0.844
Unknown	339	0.9	Unknown vs. Background	0.62 (0.17,2.22)	0.460
Low	194	1.6	Low vs. Background	1.09 (0.30,3.93)	0.901
High	183	1.6	High vs. Background	1.15 (0.32,4.17)	0.830
Total	1,487				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	771	All Categories		0.584	AGE*RACE (p=0.017)
Unknown	339	Unknown vs. Background	0.63 (0.17,2.29)	0.478	
Low	194	Low vs. Background	1.21 (0.33,4.46)	0.774	
High	183	High vs. Background	1.99 (0.52,7.57)	0.312	
Total	1,487				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-27.

Analysis of Patellar Reflex

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.0	1.12 (0.68,1.83)	0.661
	Medium	260	3.1		
	High	131	1.5		
b) Maximal (n=741)	Low	184	1.1	1.23 (0.84,1.79)	0.304
	Medium	371	1.6		
	High	186	2.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=519)	1.11 (0.67,1.85)	0.686	AGE (p=0.641) DIAB (p=0.107)
d) Maximal (n=739)	1.33 (0.89,2.00)	0.182	AGE*DIAB (p=0.021)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-27. (Continued)

Analysis of Patellar Reflex

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=521)						0.820[b]
	≤18.6	0.0 (72)	3.1 (128)	0.0 (54)	1.16 (0.48,2.80)	0.740[c]
	>18.6	1.7 (58)	2.3 (132)	2.6 (77)	1.02 (0.54,1.93)	0.945[c]
f) Maximal (n=741)						0.786[b]
	≤18.6	0.9 (106)	1.1 (191)	2.4 (83)	1.27 (0.66,2.44)	0.470[c]
	>18.6	1.3 (78)	1.7 (179)	2.9 (104)	1.13 (0.69,1.86)	0.615[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=519)			0.738[b]	AGE (p=0.718)
	≤18.6	1.19 (0.49,2.93)	0.700[c]	DIAB (p=0.099)
	>18.6	0.99 (0.52,1.91)	0.983[c]	
h) Maximal (n=739)			0.535[b]	AGE*DIAB (p=0.014)
	≤18.6	1.52 (0.75,3.11)	0.248[c]	
	>18.6	1.18 (0.72,1.96)	0.510[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-27. (Continued)

Analysis of Patellar Reflex

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	1.2	All Categories		0.434
Unknown	343	1.2	Unknown vs. Background	1.01 (0.31,3.32)	0.981
Low	196	2.0	Low vs. Background	1.79 (0.55,5.88)	0.336
High	187	2.7	High vs. Background	2.36 (0.78,7.13)	0.127
Total	1,509				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	783	All Categories		0.343	AGE (p=0.241) RACE (p=0.112)
Unknown	343	Unknown vs. Background	1.05 (0.32,3.45)	0.935	
Low	196	Low vs. Background	1.80 (0.55,5.94)	0.332	
High	187	High vs. Background	2.75 (0.89,8.50)	0.078	
Total	1,509				

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of patellar reflex abnormalities did not differ significantly among current dioxin categories in the unadjusted analysis, although the high current dioxin category had relatively more abnormalities than the other categories (Table 8-27 [i]: 1.2%, 1.2%, 2.0%, and 2.7% for the background, unknown, low, and high current dioxin categories, p=0.434). The overall contrast remained nonsignificant after adjustment for age and race (Table 8-27 [j]: p=0.343), but the high versus background contrast became marginally significant (Adj. RR=2.75, 95% C.I.: [0.89,8.50], p=0.078).

Achilles Reflex

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analyses, initial dioxin was not significantly associated with the Achilles reflex under either the minimal (Table 8-28 [a]: p=0.718) or maximal (Table 8-28 [b]: p=0.273) assumption. Adjusting for age, race, and the diabetic class-by-lifetime alcohol history interaction, the association remained nonsignificant under both assumptions (Table 8-28 [c] and [d]: p=0.698 for the minimal analysis and p=0.224 for the maximal analysis). However, because of the association between dioxin and diabetes (see Chapter 15 for a discussion of diabetes), an additional model was examined that did not adjust for diabetic class. Adjusting for age and race only (lifetime alcohol history stepped out of the model), the relative risk was marginally more than 1 under the maximal assumption (Appendix Table G-2: Adj. RR=1.26, p=0.063). The percentages of Ranch Hands in the maximal cohort with an abnormal Achilles reflex were 2.7, 6.2, and 5.4 percent for the low, medium, and high initial dioxin categories. The results under the minimal assumption remained nonsignificant after excluding diabetic class (p=0.771).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal assumption, the association between current dioxin and the Achilles reflex differed significantly between time since tour strata in the unadjusted analysis (Table 8-28 [e]: p=0.049). The relative risk was marginally less than 1 for Ranch Hands in the minimal cohort with a later tour (time$\leq$18.6: Est. RR=0.59, p=0.098) in contrast to a nonsignificant relative risk that was more than 1 for Ranch Hands in the minimal cohort with an early tour (time>18.6: Est. RR=1.17, p=0.387). The current dioxin-by-time interaction was not significant in the unadjusted maximal analysis, nor was there a significant relative risk within either time stratum.

After adjustment for age, race, and the diabetic class-by-lifetime alcohol history interaction, the interaction between current dioxin and time became marginally significant under the minimal assumption (Table 8-28 [g]: p=0.064), with neither of the within time stratum results significant. Adjusting for the same covariates, the current dioxin-by-time interaction was not significant under the maximal assumption, although the relative risk became marginally more than 1 for Ranch Hands with an early tour (time>18.6: Adj. RR=1.33, p=0.073). Adjusting for age and race only, the relative risk was significantly more than 1 in this stratum (Appendix Table G-2: Adj. RR=1.42, p=0.022).

TABLE 8-28.

Analysis of Achilles Reflex

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=520)	Low	130	6.2	0.95 (0.70,1.28)	0.718
	Medium	259	7.3		
	High	131	3.8		
b) Maximal (n=739)	Low	183	2.7	1.14 (0.91,1.42)	0.273
	Medium	370	6.2		
	High	186	5.4		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=512)	0.94 (0.68,1.29)	0.698	AGE (p=0.033) RACE (p=0.040) DIAB*DRKYR (p=0.002)
d) Maximal (n=728)	1.17 (0.91,1.49)	0.224	AGE (p=0.002) RACE (p=0.052) DIAB*DRKYR (p=0.020)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-28. (Continued)

Analysis of Achilles Reflex

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal (n=520)						0.049[b]
	≤18.6	5.6 (72)	8.7 (127)	0.0 (54)	0.59 (0.31,1.10)	0.098[c]
	>18.6	1.7 (58)	8.3 (132)	6.5 (77)	1.17 (0.82,1.69)	0.387[c]
f) Maximal (n=739)						0.305[b]
	≤18.6	2.9 (105)	6.8 (190)	2.4 (83)	0.97 (0.65,1.43)	0.861[c]
	>18.6	3.9 (78)	5.0 (179)	7.7 (104)	1.24 (0.93,1.66)	0.143[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal (n=512)			0.064[b]	AGE (p=0.039)
	≤18.6	0.61 (0.33,1.15)	0.126[c]	RACE (p=0.034)
	>18.6	1.17 (0.79,1.74)	0.425[c]	DIAB*DRKYR (p=0.002)
h) Maximal (n=728)			0.243[b]	AGE (p=0.001)
	≤18.6	0.99 (0.65,1.50)	0.950[c]	RACE (p=0.052)
	>18.6	1.33 (0.97,1.81)	0.073[c]	DIAB*DRKYR (p=0.020)

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-28. (Continued)

Analysis of Achilles Reflex

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	784	5.6	All Categories		0.290
Unknown	342	3.8	Unknown vs. Background	0.66 (0.35,1.25)	0.205
Low	195	7.7	Low vs. Background	1.40 (0.76,2.57)	0.277
High	187	5.4	High vs. Background	0.95 (0.47,1.92)	0.887
Total	1,508				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	782	All Categories		0.313**	DXCAT*RACE (p=0.045)
Unknown	341	Unknown vs. Background	0.66 (0.35,1.26)**	0.211**	AGE (p<0.001) DIAB (p=0.002)
Low	193	Low vs. Background	1.39 (0.74,2.60)**	0.303**	
High	187	High vs. Background	1.06 (0.51,2.23)**	0.871**	
Total	1,503				

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis of the Achilles reflex did not find a significant difference in the prevalences among the four categories (Table 8-28 [i]: 5.6%, 3.8%, 7.7%, and 5.4% for the background, unknown, low, and high current dioxin categories, p=0.290). The adjusted analysis detected a significant interaction between categorized current dioxin and race (Table 8-28 [j]: p=0.045). Stratified results show a marginally significant overall contrast for Blacks (Appendix Table G-1: p=0.078), but this finding may be affected by sparse data. Only two Black Ranch Hands (unknown current dioxin category) and three Black Comparisons in the background category had an abnormal Achilles reflex. None of the contrasts was significant for non-Blacks (p>0.10 for each contrast). After excluding the interaction, the overall contrast was not significant in the adjusted analysis (Table 8-28 [j]: p=0.313).

Biceps Reflex

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, no Ranch Hands had an abnormal biceps reflex. One Ranch Hand had an abnormal biceps reflex under the maximal assumption. Table 8-29 [b] shows that he was in the low initial dioxin category. No analyses were done due to sparse data.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

No current dioxin and time since tour analyses were done for the biceps reflex because there was only one Ranch Hand abnormality. Table 8-29 [d] shows that he was in the low current dioxin category with a time since tour 18.6 years or less.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis found that 10 Comparisons in the background current dioxin category had an abnormal biceps reflex (1.3%) versus 1 Ranch Hand in the unknown category (0.6%). Neither the overall contrast (Table 8-29 [e]: p=0.135) nor the unknown versus background contrast (p=0.482) was significant.

Babinski Reflex

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions there were only two Ranch Hands with an abnormal Babinski reflex. For each cohort, one was in the medium initial dioxin category and the other was in the high initial dioxin category. In the unadjusted analyses, initial dioxin was not associated with the Babinski reflex under both assumptions (Table 8-30 [a] and [b]: p=0.552 under the minimal assumption and p=0.285 under the maximal assumption). No adjusted analyses were done because of the sparse number of abnormalities.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin-by-time interaction could not be investigated because no Ranch Hands with a time since tour 18.6 years or less had an abnormal Babinski reflex. The

TABLE 8-29.

Analysis of Biceps Reflex

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)	p-Value
a) Minimal (n=521)	Low	130	0.0	--	--
	Medium	260	0.0		
	High	131	0.0		
b) Maximal (n=741)	Low	184	0.5	--	--
	Medium	371	0.0		
	High	186	0.0		

--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-29. (Continued)

Analysis of Biceps Reflex

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)	p-Value
c) Minimal						--
(n=521)	≤18.6	0.0 (72)	0.0 (128)	0.0 (54)	--	--
	>18.6	0.0 (58)	0.0 (132)	0.0 (77)	--	--
d) Maximal						--
(n=741)	≤18.6	0.9 (106)	0.0 (191)	0.0 (83)	--	--
	>18.6	0.0 (78)	0.0 (179)	0.0 (104)	--	--

--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-29. (Continued)

Analysis of Biceps Reflex

e) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	784	1.3	All Categories		0.135
Unknown	343	0.6	Unknown vs. Background	0.45 (0.10,2.08)	0.482
Low	196	0.0	Low vs. Background	--	0.212
High	187	0.0	High vs. Background	--	0.232
Total	1,510				

--: Relative risk and confidence interval not given due to the absence of abnormalities.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-30.

Analysis of Babinski Reflex

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.0	1.37 (0.51,3.73)	0.552
	Medium	260	0.4		
	High	131	0.8		
b) Maximal (n=741)	Low	184	0.0	1.62 (0.70,3.75)	0.285
	Medium	371	0.3		
	High	186	0.5		

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-30. (Continued)

Analysis of Babinski Reflex

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
c) Minimal						--
(n=521)	≤18.6	0.0 (72)	0.0 (128)	0.0 (54)	--	--
	>18.6	1.7 (58)	0.0 (132)	1.3 (77)	0.96 (0.20,4.72)	0.964[b]
d) Maximal						--
(n=741)	≤18.6	0.0 (106)	0.0 (191)	0.0 (83)	--	--
	>18.6	0.0 (78)	0.6 (179)	1.0 (104)	1.24 (0.36,4.30)	0.734[b]

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-30. (Continued)

Analysis of Babinski Reflex

e) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	784	0.3	All Categories		0.641
Unknown	343	0.6	Unknown vs. Background	2.29 (0.32,16.35)	0.712
Low	196	0.0	Low vs. Background	--	0.999
High	187	0.5	High vs. Background	2.10 (0.19,23.31)	0.948
Total	1,510				

--: Relative risk and confidence interval not given due to the absence of abnormalities.
Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

association between current dioxin and the Babinski reflex was not significant for Ranch Hands with a time since tour more than 18.6 years under both the minimal (Table 8-30 [c]: p=0.964) and maximal (Table 8-30 [d]: p=0.734) assumptions. No adjusted analyses were done due to sparse data.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast was not significant in the unadjusted categorized current dioxin analysis of the Babinski reflex (Table 8-30 [e]: p=0.641). No adjusted analysis was done because there were only five participants with an abnormal Babinski reflex (two in the background category, two in the unknown current dioxin category, and one in the high current dioxin category).

Tremor

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, initial dioxin was not associated significantly with tremor (Table 8-31 [a-d]: p>0.60 for all unadjusted and adjusted analyses).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The unadjusted current dioxin and time since tour analyses of tremor did not find a significant interaction between current dioxin and time under either the minimal (Table 8-31 [e]: p=0.402) or maximal (Table 8-31 [f]: p=0.101) assumption.

The current dioxin-by-time interaction remained nonsignificant in the adjusted minimal analysis (Table 8-31 [g]: p=0.409), but the adjusted maximal analysis detected a significant interaction among current dioxin, time, and age (Table 8-31 [h]: p=0.044). Age was categorized to explore the interaction. Stratified results revealed a significant current dioxin-by-time interaction for older Ranch Hands, those born before 1942 (Appendix Table G-1: p=0.008). The within time stratum findings showed that there was a significant increased risk of tremor associated with initial dioxin for older Ranch Hands with a later tour (time≤18.6: Adj. RR=2.96, p=0.005; % abnormal: 0.0%, 0.9%, and 11.5% for the low, medium, and high initial dioxin categories). The relative risk was less than 1, but not significant for older Ranch Hands with an early tour (time>18.6: Adj. RR=0.70, p=0.432). For younger Ranch Hands, those born in or after 1942, the current dioxin-by-time interaction was not significant (p=0.954), nor were either of the within time stratum results significant (p=0.670 for time≤18.6 and p=0.440 for time>18.6).

After excluding the interaction, the current dioxin-by-time interaction was not significant for the adjusted maximal analysis (Table 8-31 [h]: p=0.102).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of tremor abnormalities did not differ significantly among current dioxin categories in the unadjusted analysis, although the high category had the highest percentage of abnormalities (Table 8-31 [i]: 2.7%, 2.6%, 2.0%, and 3.7% for the background, unknown,

TABLE 8-31.

Analysis of Tremor

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	2.3	1.08 (0.69,1.67)	0.744
	Medium	260	2.3		
	High	131	3.1		
b) Maximal (n=741)	Low	184	2.7	1.08 (0.78,1.50)	0.643
	Medium	371	1.9		
	High	186	3.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.05 (0.66,1.66)	0.850	AGE (p=0.598)
d) Maximal (n=741)	1.08 (0.77,1.51)	0.675	AGE (p=0.861)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-31. (Continued)

Analysis of Tremor

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.402[b]
(n=521)	≤18.6	1.4 (72)	2.3 (128)	3.7 (54)	1.41 (0.71,2.79)	0.326[c]
	>18.6	1.7 (58)	2.3 (132)	3.9 (77)	0.95 (0.52,1.75)	0.877[c]
f) Maximal						0.101[b]
(n=741)	≤18.6	0.0 (106)	2.1 (191)	3.6 (83)	1.56 (0.92,2.65)	0.102[c]
	>18.6	5.1 (78)	1.7 (179)	3.9 (104)	0.87 (0.55,1.37)	0.548[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.409[b]	AGE (p=0.631)
(n=521)	≤18.6	1.35 (0.67,2.75)	0.404[c]	
	>18.6	0.92 (0.49,1.73)	0.789[c]	
h) Maximal			0.102**[b]	CURR*TIME*AGE (p=0.044)
(n=741)	≤18.6	1.53 (0.89,2.63)**	0.126**[c]	
	>18.6	0.85 (0.54,1.37)**	0.512**[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
**Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-31. (Continued)

Analysis of Tremor

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	784	2.7	All Categories		0.788
Unknown	343	2.6	Unknown vs. Background	0.98 (0.44,2.16)	0.958
Low	196	2.0	Low vs. Background	0.76 (0.26,2.23)	0.614
High	187	3.7	High vs. Background	1.41 (0.59,3.37)	0.436
Total	1,510				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	784	All Categories		0.657	AGE (p=0.089) INS (p=0.126)
Unknown	343	Unknown vs. Background	0.90 (0.40,1.99)	0.789	
Low	196	Low vs. Background	0.71 (0.24,2.10)	0.532	
High	187	High vs. Background	1.51 (0.62,3.70)	0.364	
Total	1,510				

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

low, and high current dioxin categories, p>0.40 for each contrast). All contrasts remained nonsignificant after covariate adjustment (Table 8-31 [j]: p>0.35 for each contrast).

Coordination

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

The unadjusted initial dioxin analyses of coordination did not detect a significant association (Table 8-32 [a] and [b]: p=0.414 under the minimal assumption and p=0.178 under the maximal assumption), although the percentages of abnormalities increased with initial dioxin (0.0%, 1.9%, and 2.3% for the low, medium, and high initial dioxin categories of the minimal cohort; 0.5%, 1.1%, and 2.2% for the corresponding categories of the maximal cohort).

The relative risk remained nonsignificant after adjustment for age and the diabetic class-by-lifetime alcohol history interaction (Table 8-32 [c] and [d]: p=0.296 under the minimal assumption and p=0.101 under the maximal assumption). However, because of the association between dioxin and diabetes, an additional model was examined that excluded the diabetic class-by-lifetime alcohol history interaction under both assumptions. Adjusting for age only, initial dioxin was marginally associated with coordination under the maximal assumption (Table G-2: Adj. RR=1.49, p=0.085), but the association remained nonsignificant under the minimal assumption (Adj. RR=1.41, p=0.220).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The interaction between current dioxin and time since tour was not significant in the unadjusted analyses of coordination (Table 8-32 [e] and [f]: p=0.312 under the minimal assumption and p=0.128 under the maximal assumption). The relative risk was marginally more than 1 for Ranch Hands in the maximal cohort with a later tour (time≤18.6: Est. RR=2.00, p=0.051; % abnormal: 0.0%, 0.5%, and 3.6% for the low, medium, and high current dioxin categories).

Adjusting for age, the minimal analysis did not find a significant current dioxin-by-time interaction (Table 8-32 [g]: p=0.257), although the relative risk was marginally more than 1 for Ranch Hands with a later tour (time>18.6: Adj. RR=2.14, p=0.071). Under the maximal assumption, adjusting for age and the diabetic class-by-lifetime alcohol history interaction, the current dioxin-by-time interaction was marginally significant (Table 8-32 [h]: p=0.086) and the relative risk was significantly more than 1 for Ranch Hands with a later tour (time≤18.6: Adj. RR=2.53, p=0.019). The adjusted relative risk was more than 1, but not significant for Ranch Hands in the maximal cohort with an early tour (time>18.6: Adj. RR=1.11, p=0.758).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The prevalence of coordination abnormalities differed marginally among current dioxin categories in the unadjusted analysis (Table 8-32 [i]: 0.4%, 1.2%, 1.0%, and 2.7% for the background, unknown, low, and high current dioxin categories, p=0.056). There was a significant increased risk for the high category relative to the background category (Est. RR=7.14, 95% C.I.: [1.69,30.16], p=0.007).

TABLE 8-32.

Analysis of Coordination

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.0	1.25 (0.74,2.11)	0.414
	Medium	260	1.9		
	High	131	2.3		
b) Maximal (n=740)	Low	183	0.5	1.35 (0.89,2.06)	0.178
	Medium	371	1.1		
	High	186	2.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=513)	1.35 (0.78,2.36)	0.296	AGE (p=0.050) DIAB*DRKYR (p=0.046)
d) Maximal (n=729)	1.48 (0.94,2.32)	0.101	AGE (p=0.041) DIAB*DRKYR (p=0.047)

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-32. (Continued)

Analysis of Coordination

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.312[b]
(n=521)	≤18.6	0.0 (72)	1.6 (128)	3.7 (54)	1.69 (0.75,3.79)	0.206[c]
	>18.6	1.7 (58)	0.8 (132)	2.6 (77)	0.94 (0.42,2.11)	0.885[c]
f) Maximal						0.128[b]
(n=740)	≤18.6	0.0 (105)	0.5 (191)	3.6 (83)	2.00 (1.00,4.03)	0.051[c]
	>18.6	1.3 (78)	1.1 (179)	1.9 (104)	0.99 (0.53,1.84)	0.962[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.257[b]	AGE (p=0.032)
(n=521)	≤18.6	2.14 (0.94,4.91)	0.071[c]	
	>18.6	1.14 (0.52,2.51)	0.748[c]	
h) Maximal			0.086[b]	AGE (p=0.025)
(n=729)	≤18.6	2.53 (1.16,5.48)	0.019[c]	DIAB*DRKYR (p=0.049)
	>18.6	1.11 (0.58,2.11)	0.758[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-32. (Continued)

Analysis of Coordination

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	0.4	All Categories		0.056
Unknown	342	1.2	Unknown vs. Background	3.08 (0.68,13.82)	0.143
Low	196	1.0	Low vs. Background	2.68 (0.44,16.15)	0.282
High	187	2.7	High vs. Background	7.14 (1.69,30.16)	0.007
Total	1,508				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	781	All Categories		0.006**	DXCAT*AGE (p=0.049)
Unknown	341	Unknown vs. Background	4.68 (0.84,25.97)**	0.077**	RACE (p=0.093) DIAB*INS (p=0.038)
Low	194	Low vs. Background	3.89 (0.53,28.40)**	0.180**	
High	187	High vs. Background	18.30 (3.26,102.7)**	0.001**	
Total	1,503				

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

The adjusted analysis detected a significant categorized current dioxin-by-age interaction (Table 8-32 [j]: p=0.049). Age was dichotomized to explore the interaction. There was a significant overall difference in the prevalences of coordination abnormalities among categories for older Ranch Hands, those born before 1942 (Appendix Table G-1: 0.2%, 1.3%, 0.0%, and 5.7% for the background, unknown, low, and high current dioxin categories, p=0.003). The relative risk was significantly more than 1 for the high versus background contrast (Adj. RR=32.71, 95% C.I.: [3.50,306.0], p=0.002). No contrasts were significant in the younger Ranch Hand stratum, but the background category had the fewest percentage of abnormalities (0.3%, 0.9%, 2.5%, and 0.9% for the background, unknown, low, and high current dioxin categories, p>0.10 for each contrast).

After excluding the interaction, the adjusted analysis displayed a significant overall contrast (Table 8-32 [j]: p=0.006). The high versus background contrast was significant (Adj. RR=18.30, 95% C.I.: [3.26,102.7], p=0.001) and the unknown versus background contrast was marginally significant (Adj. RR=4.68, 95% C.I.: [0.84,25.97], p=0.077).

Romberg Sign

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, there were only two assayed Ranch Hands with an abnormal Romberg sign. The association with initial dioxin was not significant (Table 8-33 [a] and [b]: p=0.871 in the unadjusted minimal analysis and p=0.479 in the unadjusted maximal analysis). No adjusted analyses were done because of the sparse number of abnormalities.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin and time since tour analyses of Romberg sign could not investigate the interaction between current dioxin and time because no Ranch Hands with a later tour had an abnormal Romberg sign. For Ranch Hands with an early tour, the association between current dioxin and Romberg sign was not significant (Table 8-33 [c] and [d]: p=0.921 for the unadjusted minimal analysis and p=0.770 for the unadjusted maximal analysis). No adjusted analyses were done due to sparse data.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast among current dioxin categories was not significant in the unadjusted analysis of Romberg sign (Table 8-33 [e]: p=0.117). The low and high current dioxin categories each had one abnormality; there were no abnormalities in the background and unknown categories. No adjusted analysis was done because of the sparse number of abnormalities.

Gait

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Although the percentages of gait abnormalities increased with initial dioxin, the relative risk was not significant in the unadjusted analyses under both the minimal (Table 8-34 [a]: Est. RR=1.27, p=0.236; % abnormal: 0.8%, 3.5%, and 3.8% for the low, medium, and high initial dioxin categories) and maximal (Table 8-34 [b]: Est. RR=1.25, p=0.154; % abnormal:

TABLE 8-33.

Analysis of Romberg Sign

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.0	1.10 (0.36,3.30)	0.871
	Medium	260	0.4		
	High	131	0.8		
b) Maximal (n=741)	Low	184	0.0	1.39 (0.58,3.34)	0.479
	Medium	371	0.3		
	High	186	0.5		

[a]Relative risk for a twofold increase in dioxin.
Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-33. (Continued)

Analysis of Romberg Sign

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
c) Minimal						--
(n=521)	≤18.6	0.0 (72)	0.0 (128)	0.0 (54)	--	--
	>18.6	0.0 (58)	0.8 (132)	1.3 (77)	0.92 (0.18,4.70)	0.921[b]
d) Maximal						--
(n=741)	≤18.6	0.0 (106)	0.0 (191)	0.0 (83)	--	--
	>18.6	0.0 (78)	0.6 (179)	1.0 (104)	1.21 (0.34,4.24)	0.770[b]

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
--: Relative risk, confidence interval, and p-value not given due to the sparse number of abnormalities.
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-33. (Continued)

Analysis of Romberg Sign

e) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	0.0	All Categories		0.117
Unknown	343	0.0	Unknown vs. Background	--	--
Low	196	0.5	Low vs. Background	--	0.400
High	187	0.5	High vs. Background	--	0.386
Total	1,509				

--: Relative risk/confidence interval/p-value not given due to the absence of abnormalities.
Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

TABLE 8-34.

Analysis of Gait

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	0.8	1.27 (0.87,1.87)	0.236
	Medium	260	3.5		
	High	131	3.8		
b) Maximal (n=740)	Low	183	1.6	1.25 (0.93,1.69)	0.154
	Medium	371	2.7		
	High	186	3.2		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=513)	1.24 (0.82,1.87)	0.323	AGE (p=0.514) DIAB (p=0.051) DRKYR (p=0.132) INS (p=0.062)
d) Maximal (n=729)	1.30 (0.94,1.80)	0.123	AGE (p=0.696) DIAB (p=0.042) DRKYR (p=0.034)

[a]Relative risk for a twofold increase in dioxin.
Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-34. (Continued)

Analysis of Gait

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.880[b]
(n=521)	≤18.6	1.4 (72)	1.6 (128)	1.9 (54)	1.18 (0.49,2.84)	0.705[c]
	>18.6	1.7 (58)	4.6 (132)	5.2 (77)	1.10 (0.69,1.73)	0.692[c]
f) Maximal						0.824[b]
(n=740)	≤18.6	1.0 (105)	1.6 (191)	2.4 (83)	1.08 (0.58,2.04)	0.806[c]
	>18.6	1.3 (78)	3.9 (179)	4.8 (104)	1.17 (0.82,1.68)	0.382[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.901[b]	AGE (p=0.720)
(n=513)	≤18.6	1.14 (0.47,2.75)	0.768[c]	DIAB (p=0.036)
	>18.6	1.07 (0.67,1.73)	0.771[c]	DRKYR (p=0.137)
				INS (p=0.053)
h) Maximal			0.949[b]	AGE (p=0.917)
(n=729)	≤18.6	1.21 (0.61,2.40)	0.577[c]	DIAB (p=0.032)
	>18.6	1.18 (0.81,1.73)	0.379[c]	DRKYR (p=0.037)

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-34. (Continued)

Analysis of Gait

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	2.2	All Categories		0.657
Unknown	342	2.6	Unknown vs. Background	1.22 (0.54,2.76)	0.637
Low	196	3.1	Low vs. Background	1.42 (0.55,3.66)	0.464
High	187	3.7	High vs. Background	1.75 (0.72,4.29)	0.219
Total	1,508				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	779	All Categories		0.482**	DXCAT*DIAB (p=0.047) AGE (p=0.135)
Unknown	338	Unknown vs. Background	1.06 (0.45,2.50)**	0.889**	DRKYR (p=0.044)
Low	192	Low vs. Background	1.50 (0.58,3.88)**	0.399**	
High	183	High vs. Background	2.03 (0.81,5.08)**	0.131**	
Total	1,492				

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

1.6%, 2.7%, and 3.2% for the low, medium, and high initial dioxin categories) assumptions. The adjusted analyses displayed essentially the same findings as the unadjusted analyses (Table 8-34 [c] and [d]: Adj. RR=1.24, p=0.323 for the minimal analysis and Adj. RR=1.30, p=0.123 for the maximal analysis).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under both the minimal and maximal assumptions, the interaction between current dioxin and time since tour was not significant in the analyses of gait (Table 8-34 [e-h]: p>0.80 in each analysis).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted categorized current dioxin analysis of gait did not find a significant overall contrast (Table 8-34 [i]: p=0.657), but the high current dioxin category had the highest percentage of abnormalities (2.2%, 2.6%, 3.1%, and 3.7% for the background, unknown, low, and high current dioxin categories). Each Ranch Hand versus background contrast was also not significant (p>0.20 for each contrast).

The adjusted analysis detected a significant categorized current dioxin-by-diabetic class interaction (Table 8-34 [j]: p=0.047). Stratified results showed a marginally significant overall contrast among categories for normal participants (Appendix Table G-1: p=0.095; 2.3%, 0.7%, 2.7%, and 4.0% for the background, unknown, low, and high current dioxin categories), although none of the Ranch Hand versus background contrasts was significant (p>0.10 for each contrast). There was also a marginally significant overall contrast for diabetically impaired individuals (p=0.052), but the only abnormalities were in the unknown (8.5%, n=47) and background (1.9%, n=107) categories; the unknown versus background contrast was marginally significant (Adj. RR=5.27, 95% C.I.: [0.92,30.11], p=0.062). The overall contrast was not significant for diabetic individuals (p=0.630), but the percentages of gait abnormalities increased with current dioxin (1.5%, 5.3%, 5.9%, and 6.5% for the background, unknown, low, and high current dioxin categories). None of the Ranch Hand versus background contrasts was significant in this stratum (p>0.25 for each contrast).

After excluding the interaction, the adjusted analysis did not reveal any significant findings (Table 8-34 [j]: p>0.10 for each contrast).

CNS Index

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

In the unadjusted analyses, initial dioxin was not significantly associated with the CNS index under the minimal assumption (Table 8-35 [a]: p=0.171), but the estimated relative risk was marginally more than 1 under the maximal assumption (Table 8-35 [b]: Est. RR=1.24, p=0.064). In the maximal cohort, the percentages of CNS abnormalities were 3.8, 4.6, and 7.0 percent for the low, medium, and high initial dioxin categories.

Under both assumptions, the adjusted analyses detected a significant initial dioxin-by-age interaction (Table 8-35 [c] and [d]: p=0.019 in the adjusted minimal analysis and p=0.044 in the adjusted maximal analysis). Age was categorized to explore the interactions. Both analyses found a significant increased risk of CNS abnormalities for older Ranch Hands,

TABLE 8-35.

Analysis of CNS Index

Ranch Hands - Log_2 (Initial Dioxin) - Unadjusted

Assumption	Initial Dioxin	n	Percent Abnormal	Est. Relative Risk (95% C.I.)[a]	p-Value
a) Minimal (n=521)	Low	130	3.1	1.23 (0.92,1.64)	0.171
	Medium	260	5.8		
	High	131	7.6		
b) Maximal (n=740)	Low	183	3.8	1.24 (0.99,1.55)	0.064
	Medium	371	4.6		
	High	186	7.0		

Ranch Hands - Log_2 (Initial Dioxin) - Adjusted

Assumption	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
c) Minimal (n=521)	1.25 (0.93,1.68)**	0.145**	INIT*AGE (p=0.019)
d) Maximal (n=731)	1.26 (1.00,1.59)**	0.050**	INIT*AGE (p=0.044) DRKYR (p=0.077)

[a]Relative risk for a twofold increase in dioxin.

**Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.

TABLE 8-35. (Continued)

Analysis of CNS Index

Ranch Hands - Log_2 (Current Dioxin) and Time - Unadjusted

Assumption	Time (Yrs.)	Percent Abnormal/(n) Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
e) Minimal						0.383[b]
(n=521)	≤18.6	2.8 (72)	4.7 (128)	7.4 (54)	1.43 (0.87,2.34)	0.159[c]
	>18.6	3.5 (58)	6.1 (132)	9.1 (77)	1.08 (0.74,1.57)	0.686[c]
f) Maximal						0.256[b]
(n=740)	≤18.6	1.0 (105)	3.7 (191)	8.4 (83)	1.44 (0.99,2.10)	0.056[c]
	>18.6	5.1 (78)	5.0 (179)	8.7 (104)	1.09 (0.82,1.46)	0.541[c]

Ranch Hands - Log_2 (Current Dioxin) and Time - Adjusted

Assumption	Time (Yrs.)	Adj. Relative Risk (95% C.I.)[a]	p-Value	Covariate Remarks
g) Minimal			0.372[b]	AGE (p=0.628)
(n=521)	≤18.6	1.47 (0.88,2.43)	0.137[c]	
	>18.6	1.11 (0.75,1.63)	0.607[c]	
h) Maximal			0.165[b]	AGE (p=0.768)
(n=731)	≤18.6	1.55 (1.05,2.31)	0.029[c]	DRKYR (p=0.074)
	>18.6	1.10 (0.82,1.48)	0.511[c]	

[a]Relative risk for a twofold increase in dioxin.
[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).
[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).
Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.

TABLE 8-35. (Continued)

Analysis of CNS Index

i) Ranch Hands and Comparisons by Current Dioxin Category - Unadjusted

Current Dioxin Category	n	Percent Abnormal	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	783	4.9	All Categories		0.276
Unknown	342	5.3	Unknown vs. Background	1.09 (0.61,1.94)	0.771
Low	196	4.6	Low vs. Background	0.94 (0.45,1.99)	0.878
High	187	8.6	High vs. Background	1.83 (1.00,3.37)	0.050
Total	1,508				

j) Ranch Hands and Comparisons by Current Dioxin Category - Adjusted

Current Dioxin Category	n	Contrast	Adj. Relative Risk (95% C.I.)	p-Value	Covariate Remarks
Background	783	All Categories		0.137**	DXCAT*AGE (p=0.018) RACE*INS (p=0.023)
Unknown	342	Unknown vs. Background	1.01 (0.56,1.81)**	0.973**	
Low	196	Low vs. Background	0.91 (0.43,1.92)**	0.798**	
High	187	High vs. Background	2.08 (1.11,3.89)**	0.023**	
Total	1,508				

**Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); adjusted relative risk, confidence interval, and p-value derived from a model fitted after deletion of this interaction.

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.

those born before 1942 (Appendix Table G-2: Adj. RR=1.66, p=0.010 in the minimal analysis and Adj. RR=1.53, p=0.009 in the maximal analysis). In both cohorts, the prevalence of abnormalities increased with initial dioxin for older Ranch Hands (2.3%, 4.0%, and 12.5% for the low, medium, and high initial dioxin categories in the minimal cohort; 2.7%, 3.3%, and 10.3% for the corresponding categories in the maximal cohort). For younger Ranch Hands, the relative risk was not significant (Adj. RR=0.87, p=0.523 in the minimal cohort; Adj. RR=1.00, p=0.976 in the maximal cohort).

After excluding the interaction, the adjusted minimal analysis was not significant (Table 8-35 [c]: p=0.145), but the adjusted maximal analysis displayed a significant increased risk (Table 8-35 [d]: Adj. RR=1.26, p=0.050).

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The unadjusted current dioxin and time since tour analyses of the CNS index did not find a significant interaction between current dioxin and time (Table 8-35 [e] and [f]: p=0.383 under the minimal assumption and p=0.256 under the maximal assumption). There was a marginally significant association between current dioxin and the CNS index for Ranch Hands with a later tour under the maximal assumption (time≤18.6: Est. RR=1.44, p=0.056; % abnormal: 1.0%, 3.7%, and 8.4% for the low, medium, and high current dioxin categories). None of the other within time stratum results was significant in the unadjusted analyses.

The adjusted analyses displayed similar findings. The current dioxin-by-time interaction was not significant under either assumption (Table 8-35 [g] and [h]: p=0.372 under the minimal assumption and p=0.165 under the maximal assumption). Under the maximal assumption, the relative risk of an abnormal CNS index was significant for Ranch Hands with a later tour (Adj. RR=1.55, p=0.029).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The overall contrast was not significant in the unadjusted categorized current dioxin analysis of the CNS index (Table 8-35 [i]: p=0.276), although there were relatively more abnormalities in the high current dioxin category than in the background category (8.6% versus 4.9%; Est. RR=1.83, 95% C.I.: [1.00,3.37], p=0.050). The percentages of abnormalities in the low (4.6%) and unknown (5.3%) current dioxin categories were not significantly different from the background percentage (p>0.75 for both contrasts).

The adjusted analysis detected a significant categorized current dioxin-by-age interaction (Table 8-35 [j]: p=0.018). Stratified results showed that the prevalence of CNS abnormalities differed significantly among current dioxin categories for older participants (Appendix Table G-1: 5.9%, 5.3%, 1.7%, and 12.9% for the background, unknown, low, and high current dioxin categories, p=0.017). For older individuals, the relative risk was significantly more than 1 for the high versus background contrast (Adj. RR=2.39, 95% C.I.: [1.07,5.34], p=0.034) and it was marginally less than 1 for the low versus background contrast (Adj. RR=0.27, 95% C.I.: [0.06,1.16], p=0.079). The overall contrast was not significant for younger men (p=0.401) although the low versus background relative risk was marginally more than 1 (Adj. RR=2.50, 95% C.I.: [0.93,6.72], p=0.069). In this stratum, the prevalences for the background, unknown, low, and high current dioxin categories were 3.4, 5.1, 8.6, and 6.0 percent. The interaction occurred partly because the low category had the

fewest percentage of abnormalities in the older age stratum, but it had the highest percentage of abnormalities in the younger age stratum.

After deleting the interaction, the adjusted analysis supported the unadjusted findings. The overall contrast was not significant (Table 8-35 [j]: p=0.137), but the high current dioxin category had a significant increased risk of CNS abnormalities (Adj. RR=2.08, 95% C.I.: [1.11,3.89], p=0.023).

Longitudinal Analysis

Physical Examination Variables

The neurological assessment conducted longitudinal analyses for the cranial nerve index and the CNS index. These analyses only included participants who were normal at the 1985 examination to determine whether the incidence between 1985 and 1987 for these two variables was associated with dioxin. The longitudinal analyses investigated the change between 1985 and 1987 because SCRF conducted both of these neurological examinations.

Cranial Nerve Index

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the longitudinal analysis found that initial dioxin was not significantly associated with the percentage of Ranch Hands who developed a cranial nerve index abnormality between the 1985 and 1987 examinations (Table 8-36 [a]: p=0.288). However, under the maximal assumption, there was a marginally significant decreased risk (Table 8-36 [b]: Est. RR= 0.83, p=0.055). The percentages of Ranch Hands in the maximal cohort with an abnormal index in 1987 (based on those who were normal in 1985) were 15.3, 12.7, and 7.3 percent for the low, medium, and high initial dioxin categories.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

Under the minimal assumption, the longitudinal analysis of the cranial nerve index did not detect a significant current dioxin-by-time since tour interaction (Table 8-36 [c]: p=0.756). Thus, the association with current dioxin did not differ between time strata.

However, under the maximal assumption, there was a marginally significant interaction between current dioxin and time (Table 8-36 [d]: p=0.086). For Ranch Hands in the maximal cohort with a later tour, the relative risk of developing a cranial nerve index abnormality between 1985 and 1987 was significantly less than 1 (time$\leq$18.6: Est. RR=0.68, p=0.017; % abnormal: 19.8%, 11.7%, and 6.6% for the low, medium, and high current dioxin categories).

The relative risk was less than 1, but not significant for Ranch Hands in the maximal cohort with an early tour (time>18.6: Est. RR=0.97, p=0.816).

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The percentage of participants who developed a cranial nerve index abnormality between the 1985 and 1987 examinations did not differ significantly among the four current

TABLE 8-36.

Longitudinal Analysis of Cranial Nerve Index

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	Percent Abnormal/(n) Examination 1982	1985	1987
a) Minimal	Low	51.8 (114)	6.6 (121)	12.4 (121)
	Medium	52.8 (231)	7.2 (251)	15.5 (251)
	High	58.3 (115)	8.0 (125)	12.8 (125)

	Normal in 1985			
Initial Dioxin	n in 1987	Percent Abnormal in 1987	Est. Relative Risk (95% C.I.)[a]	p-Value
Low	113	10.6	0.87 (0.67,1.13)	0.288
Medium	233	12.5		
High	115	7.8		

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Summary statistics for 1982 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1985 and 1987 results. Statistical analyses are based only on participants who were normal in 1985 (see Chapter 4, Statistical Methods).

TABLE 8-36. (Continued)

Longitudinal Analysis of Cranial Nerve Index

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	Percent Abnormal/(n) Examination 1982	1985	1987
b) Maximal	Low	52.3 (155)	12.8 (172)	18.6 (172)
	Medium	52.5 (326)	6.8 (355)	15.2 (355)
	High	56.4 (163)	7.3 (177)	11.9 (177)

Initial Dioxin	Normal in 1985: n in 1987	Normal in 1985: Percent Abnormal in 1987	Est. Relative Risk (95% C.I.)[a]	p-Value
Low	150	15.3	0.83 (0.69,1.01)	0.055
Medium	331	12.7		
High	164	7.3		

[a]Relative risk for a twofold increase in dioxin.

Note: Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.
Summary statistics for 1982 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1985 and 1987 results. Statistical analyses are based only on participants who were normal in 1985 (see Chapter 4, Statistical Methods).

TABLE 8-36. (Continued)

Longitudinal Analysis of Cranial Nerve Index

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Percent Abnormal/(n) Current Dioxin Low	Medium	High
c) Minimal	≤18.6	1982	54.7 (64)	52.2 (113)	52.2 (46)
		1985	7.6 (66)	8.3 (121)	0.0 (50)
		1987	10.6 (66)	16.5 (121)	4.0 (50)
	>18.6	1982	49.0 (49)	55.5 (119)	58.0 (69)
		1985	5.4 (56)	6.2 (129)	13.3 (75)
		1987	12.5 (56)	16.3 (129)	17.3 (75)

Time (Yrs.)	Normal in 1985: Percent Abnormal/(n) in 1987 Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
					0.756[b]
≤18.6	9.8 (61)	11.7 (111)	4.0 (50)	0.77 (0.48,1.23)	0.278[c]
>18.6	11.3 (53)	14.1 (121)	9.2 (65)	0.84 (0.60,1.19)	0.338[c]

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Summary statistics for 1982 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1985 and 1987 results. Statistical analyses are based only on participants who were normal in 1985 (see Chapter 4, Statistical Methods).

TABLE 8-36. (Continued)

Longitudinal Analysis of Cranial Nerve Index

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Percent Abnormal/(n) Current Dioxin Low	Medium	High
d) Maximal	≤18.6	1982	46.0 (87)	54.4 (169)	51.4 (72)
		1985	11.3 (97)	7.9 (177)	2.6 (78)
		1987	21.7 (97)	14.7 (177)	7.7 (78)
	>18.6	1982	56.1 (66)	52.5 (158)	59.8 (92)
		1985	14.5 (76)	5.7 (176)	11.0 (100)
		1987	14.5 (76)	15.9 (176)	15.0 (100)

Time (Yrs.)	Normal in 1985: Percent Abnormal/(n) in 1987 Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
					0.086[b]
≤18.6	19.8 (86)	11.7 (163)	6.6 (76)	0.68 (0.50,0.93)	0.017[c]
>18.6	7.7 (65)	14.5 (166)	7.9 (89)	0.97 (0.75,1.25)	0.816[c]

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.
Summary statistics for 1982 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1985 and 1987 results. Statistical analyses are based only on participants who were normal in 1985 (see Chapter 4, Statistical Methods).

TABLE 8-36. (Continued)

Longitudinal Analysis of Cranial Nerve Index

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	Percent Abnormal/(n) Examination 1982	1985	1987
Background	52.0 (641)	9.0 (733)	16.1 (733)
Unknown	50.0 (286)	10.6 (320)	15.6 (320)
Low	52.8 (176)	7.4 (190)	17.9 (190)
High	56.1 (164)	7.3 (178)	11.8 (178)

Current Dioxin Category	Normal in 1985: n in 1987	Normal in 1985: Percent Abnormal in 1987	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	667	12.7	All Categories		0.125
Unknown	286	13.3	Unknown vs. Background	1.05 (0.70,1.58)	0.818
Low	176	14.8	Low vs. Background	1.19 (0.74,1.91)	0.479
High	165	7.3	High vs. Background	0.54 (0.29,1.01)	0.053

Note: Background (Comparisons): Current Dioxin $\leq$10 ppt.
Unknown (Ranch Hands): Current Dioxin $\leq$10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin $\leq$33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.
Summary statistics for 1982 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1985 and 1987 results. Statistical analyses are based only on participants who were normal in 1985 (see Chapter 4, Statistical Methods).

dioxin categories in the longitudinal analysis (Table 8-36 [e]: 12.7%, 13.3%, 14.8%, and 7.3% for the background, unknown, low, and high current dioxin categories, p=0.125). However, the relative risk of developing an abnormal cranial nerve index for the high versus background contrast was marginally less than 1 (Est. RR=0.54; 95% C.I.: [0.29,1.01], p=0.053).

CNS Index

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under the minimal assumption, the longitudinal analysis of the CNS index did not find a significant risk associated with initial dioxin (Table 8-37 [a]: Est. RR=1.25, p=0.207), but the relative risk was marginally significant under the maximal assumption (Table 8-37 [b]: Est. RR=1.27, p=0.087). The percentages of Ranch Hands in the maximal cohort with an abnormal CNS index at the 1987 examination (based on those who were normal at the 1985 examination) were 2.4, 3.5, and 5.2 percent for the low, medium, and high initial dioxin categories.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin-by-time since tour interaction was not significant for the longitudinal analysis of the CNS index under either the minimal or the maximal assumption (Table 8-37 [c] and [d]: p=0.654 and p=0.409, respectively). However, under the maximal assumption, the relative risk was marginally more than 1 for Ranch Hands with a later tour (time$\leq$18.6: Est. RR=1.45, p=0.080). For these Ranch Hands, the percentages with an abnormal CNS index (based on those who were normal in 1985) were 1.0, 2.9, and 7.8 percent for the low, medium, and high current dioxin categories.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The longitudinal analysis did not find a significant difference in the percentages of participants with an abnormal CNS index at the 1987 examination (based on those who were normal in 1985) among the current dioxin categories (Table 8-37 [e]: 4.4%, 3.8%, 3.2%, and 6.8% for the background, unknown, low, and high current dioxin categories, p=0.382). The three Ranch Hand versus background contrasts were also not significant (p>0.15 for each contrast).

DISCUSSION

Although definitive diagnosis usually requires laboratory testing beyond the scope of the current study, the data analyzed in this chapter can be relied upon to detect the presence, if not the cause, of neurologic disease, including disorders of the peripheral nervous system. In clinical practice, the neurological assessment can be divided into examinations of the peripheral and the cranial nerves. The central, cranial, and peripheral nerve variables examined can provide specific clues in the anatomic site of neurological lesions and clarify the need for additional diagnostic studies.

As indices of CNS function, tremor and coordination are less specific and more subject to individual variation in the absence of underlying neurological disease. Tremor, for example, may occur as a benign familial trait, may be reflective of alcohol withdrawal, or may be a marker of extrapyramidal motor system disease as in Parkinson's syndrome. The Romberg sign may signal a lesion in the cerebellum but is more often indicative of impaired position

TABLE 8-37.

Longitudinal Analysis of CNS Index

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	Percent Abnormal/(n) Examination 1982	1985	1987
a) Minimal	Low	30.6 (121)	5.6 (125)	3.2 (125)
	Medium	27.8 (245)	3.5 (255)	5.9 (255)
	High	24.0 (121)	3.9 (128)	7.8 (128)

Initial Dioxin	Normal in 1985: n in 1987	Normal in 1985: Percent Abnormal in 1987	Est. Relative Risk (95% C.I.)[a]	p-Value
Low	118	2.5	1.25 (0.89,1.75)	0.207
Medium	246	4.1		
High	123	5.7		

[a]Relative risk for a twofold increase in dioxin.

Note: Minimal--Low: 52-93 ppt; Medium: >93-292 ppt; High: >292 ppt.
Summary statistics for 1982 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1985 and 1987 results. Statistical analyses are based only on participants who were normal in 1985 (see Chapter 4, Statistical Methods).

TABLE 8-37. (Continued)

Longitudinal Analysis of CNS Index

Ranch Hands - Log_2 (Initial Dioxin)

Assumption	Initial Dioxin	Percent Abnormal/(n) Examination 1982	1985	1987
b) Maximal	Low	22.3 (166)	2.9 (175)	4.0 (175)
	Medium	28.1 349)	3.6 (361)	4.7 (361)
	High	25.7 (171)	4.4 (182)	7.1 (182)

	Normal in 1985			
Initial Dioxin	n in 1987	Percent Abnormal in 1987	Est. Relative Risk (95% C.I.)[a]	p-Value
Low	170	2.4	1.27 (0.97,1.65)	0.087
Medium	348	3.5		
High	174	5.2		

[a]Relative risk for a twofold increase in dioxin.

Note: Maximal--Low: 25-56.9 ppt; Medium: >56.9-218 ppt; High: >218 ppt.
Summary statistics for 1982 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1985 and 1987 results. Statistical analyses are based only on participants who were normal in 1985 (see Chapter 4, Statistical Methods).

TABLE 8-37. (Continued)

Longitudinal Analysis of CNS Index

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Percent Abnormal/(n) Current Dioxin Low	Medium	High
c) Minimal	≤18.6	1982	23.9 (67)	27.7 (119)	20.4 (49)
		1985	5.9 (68)	3.2 (125)	3.9 (51)
		1987	2.9 (68)	4.8 (125)	7.8 (51)
	>18.6	1982	37.0 (54)	27.6 (127)	28.2 (71)
		1985	5.3 (57)	3.1 (130)	5.2 (77)
		1987	3.5 (57)	6.2 (130)	9.1 (77)

Time (Yrs.)	Normal in 1985: Percent Abnormal/(n) in 1987 Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
					0.654[b]
≤18.6	3.1 (64)	4.1 (121)	6.1 (49)	1.39 (0.81,2.39)	0.230[c]
>18.6	0.0 (54)	4.8 (126)	5.5 (73)	1.18 (0.75,1.87)	0.473[c]

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Minimal--Low: >10-14.65 ppt; Medium: >14.65-45.75 ppt; High: >45.75 ppt.
Summary statistics for 1982 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1985 and 1987 results. Statistical analyses are based only on participants who were normal in 1985 (see Chapter 4, Statistical Methods).

TABLE 8-37. (Continued)

Longitudinal Analysis of CNS Index

Ranch Hands - Log_2 (Current Dioxin) and Time

Assumption	Time (Yrs.)	Examination	Percent Abnormal/(n) Current Dioxin Low	Medium	High
d) Maximal	≤18.6	1982	18.7 (91)	25.7 (179)	24.0 (75)
		1985	2.0 (99)	4.4 (183)	3.8 (80)
		1987	1.0 (99)	3.8 (183)	8.8 (80)
	>18.6	1982	25.7 (74)	30.4 (171)	28.1 (96)
		1985	2.6 (76)	4.0 (177)	3.9 (103)
		1987	5.3 (76)	5.1 (177)	8.7 (103)

Time (Yrs.)	Normal in 1985: Percent Abnormal/(n) in 1987 Current Dioxin Low	Medium	High	Est. Relative Risk (95% C.I.)[a]	p-Value
≤18.6	1.0 (97)	2.9 (175)	7.8 (77)	1.45 (0.96,2.21)	0.409[b] 0.080[c]
>18.6	2.7 (74)	2.9 (170)	6.1 (99)	1.15 (0.80,1.66)	0.448[c]

[a]Relative risk for a twofold increase in dioxin.

[b]Test of significance for homogeneity of relative risks (current dioxin continuous, time categorized).

[c]Test of significance for relative risk equal to 1 (current dioxin continuous, time categorized).

Note: Maximal--Low: >5-9.01 ppt; Medium: >9.01-33.3 ppt; High: >33.3 ppt.
Summary statistics for 1982 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1985 and 1987 results. Statistical analyses are based only on participants who were normal in 1985 (see Chapter 4, Statistical Methods).

TABLE 8-37. (Continued)

Longitudinal Analysis of CNS Index

e) Ranch Hands and Comparisons by Current Dioxin Category

Current Dioxin Category	Percent Abnormal/(n) Examination 1982	1985	1987
Background	26.4 (666)	3.1 (748)	5.0 (748)
Unknown	23.7 (304)	3.4 (327)	5.5 (327)
Low	27.1 (188)	3.6 (193)	4.7 (193)
High	26.3 (171)	3.8 (183)	8.7 (183)

Current Dioxin Category	Normal in 1985: n in 1987	Normal in 1985: Percent Abnormal in 1987	Contrast	Est. Relative Risk (95% C.I.)	p-Value
Background	725	4.4	All Categories		0.382
Unknown	316	3.8	Unknown vs. Background	0.85 (0.43,1.68)	0.649
Low	186	3.2	Low vs. Background	0.72 (0.30,1.75)	0.472
High	176	6.8	High vs. Background	1.58 (0.80,3.14)	0.187

Note: Background (Comparisons): Current Dioxin ≤10 ppt.
Unknown (Ranch Hands): Current Dioxin ≤10 ppt.
Low (Ranch Hands): 15 ppt < Current Dioxin ≤33.3 ppt.
High (Ranch Hands): Current Dioxin >33.3 ppt.
Summary statistics for 1982 are provided for reference purposes for participants who attended the Baseline, 1985, and 1987 examinations. P-values given are in reference to a contrast of 1985 and 1987 results. Statistical analyses are based only on participants who were normal in 1985 (see Chapter 4, Statistical Methods).

sense in the lower extremities or of inner ear disease. Finally, the mental status examination is important in the CNS assessment. Extensive psychometric studies were conducted, as in previous examination cycles, and are reported in Chapter 9.

Of the eight historical variables analyzed, only the ICD-9-CM category of "other neurologic disorders" was found to have a significant positive association with the body burden of dioxin. In the maximal cohort, a statistically significant increase in the diseases included in this category was noted in association with the extrapolated initial level of serum dioxin. Also, for Ranch Hands with less than 18.6 years since service in Vietnam, there was a significant association with current levels of serum dioxin. These positive findings were no longer present after adjustment for age and military occupation. There was no apparent increase in the historical incidence of peripheral neuropathy in association with serum dioxin levels or in Ranch Hand participants relative to Comparisons. The serum dioxin analyses did not find a significant association with an increased risk of hereditary and degenerative diseases. This finding contrasted with the results from the previous report (36), which found that the incidence of hereditary and degenerative diseases differed significantly between the Ranch Hand and Comparison groups (5.5% versus 3.5%).

Related to the extrapolated initial level of serum dioxin, there were no significant associations noted in any of the directly measured physical examination variables. Several indices (neck range of motion and cranial nerve index) were found to have statistically significant but inconsistent associations with the current level of serum dioxin without evidence for a dose-response effect. Participants more removed from their tour of duty in Vietnam were at slightly greater risk. Significant differences between current dioxin categories were not noted in either index.

Of the neurological disorders considered, only peripheral neuropathy has been clearly shown to be associated with TCDD exposure in other studies. Of the eight peripheral motor and sensory indices examined, no significant associations were found with the initial, current serum dioxin levels, or categorical dioxin levels.

In the adjusted analysis of the current serum dioxin, participants less removed from active duty in Vietnam were more likely to show abnormalities in coordination and in the CNS index in a pattern consistent with a dose-response effect. Further, for both indices, Ranch Hands with higher levels of serum dioxin were at increased risk relative to Comparisons, particularly with respect to coordination (Adj. RR=18.30; p=0.001). In the longitudinal analysis of the CNS index under the maximal assumption, there was a marginally significant positive association with initial dioxin. Ranch Hands with the highest levels of initial dioxin had a higher incidence of abnormalities (5.2%) than those in the medium (3.5%) or low (2.4%) initial dioxin categories. Though it would be difficult to explain these results on the basis of cause and effect, they are consistent with those described in the 1987 report and will be evaluated in future examination cycles.

In summary, data analyzed in this chapter revealed no consistent evidence for clinically significant neurological disease associated with the current body burden of dioxin. Statistically significant associations were noted but not in patterns consistent with a dose-response effect.

SUMMARY

The neurological assessment focused on extensive physical examination data for cranial nerve function, peripheral nerve status, and CNS coordination processes. Verified histories of neurological diseases were also examined. Three sets of analyses were performed to assess the association between dioxin and the neurological variables. Table 8-38 summarizes the results of the initial dioxin analyses. Table 8-39 presents the results of the current dioxin and time since tour analyses, and Table 8-40 summarizes the categorized current dioxin analyses. Table 8-41 lists the dioxin-by-covariate interactions found in the adjusted analyses.

Questionnaire Variables

Information from the questionnaire was verified and grouped into eight categories of neurological diseases: inflammatory diseases, hereditary and degenerative diseases, peripheral disorders, disorders of the eye, external otitis, tympanic membrane disorders, hearing loss, and other neurological diseases.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, initial dioxin was not significantly associated with inflammatory diseases, hereditary and degenerative diseases, peripheral disorders, eye disorders, tympanic membrane disorder, and otitis. There was a marginally significant increased risk of hearing loss under the minimal assumption after adjustment for age, but the relative risk was not significant under the maximal assumption.

Under both assumptions, initial dioxin was associated with a significant increased risk of conditions in the other neurological disorders category after adjusting for age. However, further investigation indicated that this was related to a significant association between occupation and other neurological disorders. Independent of group membership, officers had a much lower incidence of other neurological disorders than either enlisted flyers or enlisted groundcrew. Ranch Hand officers also had the lowest levels of dioxin in general. After adjusting for age and occupation, the association between initial dioxin and other neurological disorders became nonsignificant under both assumptions.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin and time since tour analyses were generally not significant for the questionnaire variables. Under the maximal assumption, the association between current dioxin and otitis differed significantly between time strata, but this was due to a significant decreased risk of otitis for Ranch Hands with a later tour. Adjusting for age, current dioxin was significantly associated with other neurological disorders in both time strata under the maximal assumption, but these associations became nonsignificant when occupation was included in the model.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The categorized current dioxin analyses of the questionnaire variables displayed few significant results. The unadjusted analyses found a marginally significant difference in the prevalence of hearing loss among the four current dioxin categories, with a significant decreased risk in the high category relative to the background category. Ranch Hands in the

TABLE 8-38.

Summary of Initial Dioxin Analyses for Neurological Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Unadjusted		Adjusted	
Variable	Minimal	Maximal	Minimal	Maximal
Questionnaire				
Inflammatory Diseases	NS	NS	--	--
Hereditary and Degenerative Diseases	ns	ns	ns	ns
Peripheral Disorders	NS	NS	NS	NS
Disorders of the Eye	NS	NS	NS	NS
Tympanic Membrane Disorder	ns	NS	ns	NS
Otitis	NS	ns	NS	ns
Hearing Loss	ns	ns	NS*	NS
Other Neurological Disorders	NS	+<0.001	+0.037[a]	+<0.001[a]
Other Neurological Disorders	--	--	ns[b]	NS[b]
Physical Examination				
Cranial Nerve Function				
Smell	ns	ns	ns	ns
Visual Fields	--	--	--	--
Light Reaction	NS	ns	NS	ns
Ocular Movement	ns	NS	NS	NS
Facial Sensation	ns	NS	ns	NS
Smile	NS	NS	NS	NS
Palpebral Fissure	NS	NS	NS	NS
Balance[c]	NS	NS	--	--
Speech	--	--	--	--
Neck Range of Motion	NS	ns	*** (NS*)	*** (NS)
Cranial Nerve Index	NS	ns	NS*	** (NS)
Cranial Nerve Index Without Range of Motion	NS	NS	NS	NS
Peripheral Nerve Status				
Pin Prick	NS	NS	** (NS)	** (NS)
Light Touch	ns	NS	NS	ns
Muscle Status	NS	NS	NS	NS
Vibration	ns	NS	ns	NS
Patellar Reflex	NS	NS	NS	NS
Achilles Reflex	ns	NS	ns	NS

TABLE 8-38. (Continued)

Summary of Initial Dioxin Analyses for Neurological Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

Variable	Unadjusted		Adjusted	
	Minimal	Maximal	Minimal	Maximal
Peripheral Nerve Status (continued)				
Achilles Reflex[d]	--	--	NS	NS*
Biceps Reflex	--	--	--	--
Babinski Reflex	NS	NS	--	--
Central Nervous System Coordination Processes				
Tremor	NS	NS	NS	NS
Coordination	NS	NS	NS	NS
Coordination[d]	--	--	NS	NS*
Romberg Sign[c]	NS	NS	--	--
Gait	NS	NS	NS	NS
CNS Index	NS	NS*	** (NS)	** (+0.050)

[a]Adjusted for age.

[b]Adjusted for age and occupation. Appendix Table G-3 presents a detailed description of these analyses.

[c]Balance same as Romberg sign.

[d]Adjusted results presented for model without diabetic class. Appendix Table G-2 presents a detailed description of this analysis.

+: Relative risk 1.00 or greater.

--: Analysis not applicable or not performed due to the sparse number of abnormalities.

NS/ns: Not significant ($p>0.10$).

NS*/ns*: Marginally significant ($0.05<p\leq0.10$).

** (NS)/** (ns): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.

** (0.050): Log_2 (initial dioxin)-by-covariate interaction ($0.01<p\leq0.05$); significant ($p=0.050$) when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.

*** (NS): Log_2 (initial-dioxin)-by-covariate interaction ($p\leq0.01$); not significant when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.

*** (NS*): Log_2 (initial dioxin)-by-covariate interaction ($p\leq0.01$); marginally significant when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.

Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater; a lowercase "ns" denotes relative risk less than 1.00.

TABLE 8-39.

Summary of Current Dioxin and Time Analyses for Neurological Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Unadjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Questionnaire						
Inflammatory Diseases	--	--	--	--	--	--
Hereditary and Degenerative Diseases	NS	ns	NS	NS	ns	NS
Peripheral Disorders	NS	ns	NS	NS	ns	NS
Disorders of the Eye	NS	NS	NS	NS	NS	NS
Tympanic Membrane Disorder	ns	NS	ns	ns	ns	ns
Otitis	NS	ns	ns	+0.032	-0.012	ns
Hearing Loss	NS	ns	ns	ns	ns	ns*
Other Neurological Disorders	ns	NS	NS	ns	+0.002	NS
Physical Examination						
Cranial Nerve Function						
Smell	--	ns	--	--	ns	--
Visual Fields	--	--	--	--	--	--
Light Reaction	--	ns	--	NS	ns	NS
Ocular Movement	--	--	ns	--	--	ns
Facial Sensation	--	NS	--	--	NS	--
Smile	--	--	NS*	--	--	NS
Palpebral Fissure	NS	ns	NS	NS	ns	NS
Balance[a]	--	--	ns	--	--	NS
Speech	--	--	--	--	--	--
Neck Range of Motion	NS	ns	NS	+0.024	-0.024	NS
Cranial Nerve Index	NS	ns	NS	+0.021	-0.027	NS
Cranial Nerve Index Without Range of Motion	NS	ns	NS	NS	ns	NS
Peripheral Nerve Status						
Pin Prick	NS	ns	NS	NS	NS	NS
Light Touch	+0.023	ns	NS	NS	ns	NS
Muscle Status	ns	NS	ns	ns	NS	NS
Vibration	ns	ns	ns	ns	NS	ns
Patellar Reflex	ns	NS	NS	ns	NS	NS

TABLE 8-39. (Continued)

Summary of Current Dioxin and Time Analyses for Neurological Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Unadjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Peripheral Nerve Status (continued)						
Achilles Reflex	+0.049	ns*	NS	NS	ns	NS
Biceps Reflex	--	--	--	--	--	--
Babinski Reflex	--	--	ns	--	--	NS
Central Nervous System Coordination Processes						
Tremor	ns	NS	ns	ns	NS	ns
Coordination	ns	NS	ns	ns	NS*	ns
Romberg Sign[a]	--	--	ns	--	--	NS
Gait	ns	NS	NS	NS	NS	NS
CNS Index	ns	NS	NS	ns	NS*	NS

[a]Balance same as Romberg sign.

+: C*T: Relative risk for ≤18.6 category less than relative risk for <18.6 category.
≤18.6: Relative risk 1.00 or greater.

-: ≤18.6: Relative risk less than 1.00.

--: Analysis not performed due to the sparse number of abnormalities.

NS/ns: Not significant (p>0.10).

NS*/ns*: Marginally significant (0.05<p≤0.10).

Note: P-value given if p≤0.05.
C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.
≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.
>18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.
A capital "NS" denotes relative risk for ≤18.6 category less than relative risk for >18.6 category or relative risk 1.00 or greater; a lowercase "ns" denotes relative risk for <18.6 category greater than relative risk for >18.6 category or relative risk less than 1.00.

TABLE 8-39. (Continued)

Summary of Current Dioxin and Time Analyses for Neurological Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Adjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Questionnaire						
Inflammatory Diseases	--	--	--	--	--	--
Hereditary and Degenerative Diseases	NS	ns	NS	NS	NS	NS
Peripheral Disorders	NS	ns	NS	NS	ns	NS
Disorders of the Eye	NS	NS	NS	NS	NS	NS
Tympanic Membrane Disorder	ns	NS	ns	ns	NS	ns
Otitis	NS	ns	NS	+0.031	-0.020	NS
Hearing Loss	NS	NS	NS	ns	NS	NS
Other Neurological Disorders[b]	ns	+0.041	NS	ns*	+<0.001	+0.014
Other Neurological Disorders[c]	ns	NS	ns	ns	NS	ns
Physical Examination						
Cranial Nerve Function						
Smell	--	--	--	--	--	--
Visual Fields	--	--	--	--	--	--
Light Reaction	--	--	--	--	--	--
Ocular Movement	--	--	--	--	--	--
Facial Sensation	--	--	--	--	--	--
Smile	--	--	--	--	--	--
Palpebral Fissure	NS	ns	NS	NS	ns	NS
Balance[a]	--	--	--	--	--	--
Speech	--	--	--	--	--	--
Neck Range of Motion	NS	NS	+0.017	+0.026	ns	+0.029
Cranial Nerve Index	NS	NS	+0.033	+0.023	ns	+0.034
Cranial Nerve Index Without Range of Motion	NS	ns	NS	NS	ns	NS
Peripheral Nerve Status						
Pin Prick	** (NS)	** (ns)	** (NS)	** (NS)	** (NS)	** (NS)
Light Touch	+0.048	ns	NS	NS	ns	NS
Muscle Status	ns	NS	NS	ns	NS	NS
Vibration	ns	ns	ns	ns	NS	NS

TABLE 8-39. (Continued)

Summary of Current Dioxin and Time Analyses for Neurological Variables Based on Minimal and Maximal Assumptions (Ranch Hands Only)

	Adjusted					
	Minimal			Maximal		
Variable	C*T	≤18.6	>18.6	C*T	≤18.6	>18.6
Peripheral Nerve Status (continued)						
Patellar Reflex	ns	NS	ns	ns	NS	NS
Achilles Reflex	NS*	ns	NS	NS	ns	NS*
Biceps Reflex	--	--	--	--	--	--
Babinski Reflex	--	--	--	--	--	--
Central Nervous System Coordination Processes						
Tremor	ns	NS	ns	** (ns)	** (NS)	** (ns)
Coordination	ns	NS*	NS	ns*	+0.019	NS
Romberg Sign[a]	--	--	--	--	--	--
Gait	ns	NS	NS	ns	NS	NS
CNS Index	ns	NS	NS	ns	+0.029	NS

[a]Balance same as Romberg sign.
[b]Adjusted for age.
[c]Adjusted for age and occupation. Appendix Table G-3 presents a detailed description of these analyses.
+: C*T: Relative risk for ≤18.6 category less than relative risk for >18.6 category.
≤18.6 or >18.6: Relative risk 1.00 or greater.
-: ≤18.6: Relative risk less than 1.00.
--: Analysis not performed due to the sparse number of abnormalities.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05<p\leq0.10$).
** (NS)/** (ns): Log_2 (current dioxin)-by-time-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.
Note: P-value given if $p\leq0.05$.
C*T: Log_2 (current dioxin)-by-time interaction hypothesis test.
≤18.6: Log_2 (current dioxin) hypothesis test for Ranch Hands with time since end of tour of 18.6 years or less.
>18.6: Log_2 (current) hypothesis test for Ranch Hands with time since end of tour greater than 18.6 years.
A capital "NS" denotes relative risk for ≤18.6 category less than relative risk for >18.6 category or relative risk 1.00 or greater; a lowercase "ns" denotes relative risk for ≤18.6 category greater than relative risk for >18.6 category or relative risk less than 1.00.

TABLE 8-40.

Summary of Categorized Current Dioxin Analyses for Neurological Variables (Ranch Hands and Comparisons)

Variable	All	Unadjusted: Unknown versus Background	Unadjusted: Low versus Background	Unadjusted: High versus Background
Questionnaire				
Inflammatory Diseases	NS	NS	ns	NS
Hereditary and Degenerative Diseases	NS	NS	ns	ns
Peripheral Disorders	NS	ns	ns	NS
Disorders of the Eye	NS	NS	NS	NS
Tympanic Membrane Disorder	NS	ns	NS	NS
Otitis	NS	NS	NS	ns
Hearing Loss	NS*	ns	ns	-0.009
Other Neurological Disorders	0.014	ns*	NS*	NS
Physical Examination				
Cranial Nerve Function				
Smell	NS	ns	NS	ns
Visual Fields	NS	ns	ns	ns
Light Reaction	NS	ns	ns	NS
Ocular Movement	NS	ns	NS	ns
Facial Sensation	NS	ns	ns	ns
Smile	NS	ns	ns	ns
Palpebral Fissure	NS	ns	NS	NS
Balance[a]	NS	--	NS	NS
Speech	NS	ns	NS	ns
Neck Range of Motion	NS	NS	NS	ns
Cranial Nerve Index	NS	ns	NS	ns
Cranial Nerve Index Without Range of Motion	NS	ns	NS	ns
Peripheral Nerve Status				
Pin Prick	NS	ns	ns	NS
Light Touch	NS	ns	ns	ns
Muscle Status	NS	ns	ns	ns
Vibration	NS	ns	NS	NS
Patellar Reflex	NS	NS	NS	NS

TABLE 8-40. (Continued)

Summary of Categorized Current Dioxin Analyses for Neurological Variables (Ranch Hands and Comparisons)

	Unadjusted			
Variable	All	Unknown versus Background	Low versus Background	High versus Background
Peripheral Nerve Status (continued)				
Achilles Reflex	NS	ns	NS	ns
Biceps Reflex	NS	ns	ns	ns
Babinski Reflex	NS	NS	ns	NS
Central Nervous System Coordination Processes				
Tremor	NS	ns	ns	NS
Coordination	NS*	NS	NS	+0.007
Romberg Sign[a]	NS	--	NS	NS
Gait	NS	NS	NS	NS
CNS Index	NS	NS	ns	+0.050

[a]Balance same as Romberg sign.
+: Relative risk 1.00 or greater.
-: Relative risk less than 1.00.
--: Analysis not performed due to the absence of abnormalities.
NS/ns: Not significant ($p>0.10$).
NS*/ns*: Marginally significant ($0.05<p\leq0.10$).
Note: P-value given if $p\leq0.05$.
A capital "NS" denotes relative risk 1.00 or greater; a lowercase "ns" denotes relative risk less than 1.00; a capital "NS" in the first column does not imply directionality.

TABLE 8-40. (Continued)

Summary of Categorized Current Dioxin Analyses for Neurological Variables (Ranch Hands and Comparisons)

Variable	All	Adjusted: Unknown versus Background	Adjusted: Low versus Background	Adjusted: High versus Background
Questionnaire				
Inflammatory Diseases	--	--	--	--
Hereditary and Degenerative Diseases	NS	NS	ns	ns
Peripheral Disorders	NS	ns	ns	NS
Disorders of the Eye	NS	NS	NS	NS
Tympanic Membrane Disorder	NS	ns	NS	NS
Otitis	NS	NS	NS	ns
Hearing Loss	NS	ns	ns	ns
Other Neurological Disorders[b]	<0.001	-0.041	NS*	+0.005
Other Neurological Disorders[c]	NS	NS	NS	NS
Physical Examination				
Cranial Nerve Function				
Smell	NS	ns	NS	--
Visual Fields	--	--	--	--
Light Reaction	NS	ns	--	NS
Ocular Movement	NS	ns	NS	--
Facial Sensation	NS	--	ns	ns
Smile	NS	ns	ns	NS
Palpebral Fissure	NS	ns	NS	NS
Balance[a]	--	--	--	--
Speech	--	--	--	--
Neck Range of Motion	** (NS)	** (ns)	** (NS)	** (NS)
Cranial Nerve Index	NS	ns	NS	ns
Cranial Nerve Index Without Range of Motion	** (NS)	** (ns*)	** (NS)	** (ns)
Peripheral Nerve Status				
Pin Prick	NS	ns	ns	NS
Light Touch	NS	NS	ns	ns
Muscle Status	** (NS)	** (ns)	** (ns)	** (NS)
Vibration	NS	ns	NS	NS

TABLE 8-40. (Continued)

Summary of Categorized Current Dioxin Analyses for Neurological Variables (Ranch Hands and Comparisons)

Variable	All	Adjusted: Unknown versus Background	Adjusted: Low versus Background	Adjusted: High versus Background
Peripheral Nerve Status (continued)				
Patellar Reflex	NS	NS	NS	NS*
Achilles Reflex	** (NS)	** (ns)	** (NS)	** (NS)
Biceps Reflex	--	--	--	--
Babinski Reflex	--	--	--	--
Central Nervous System Coordination Processes				
Tremor	NS	ns	ns	NS
Coordination	** (0.006)	** (NS*)	** (NS)	** (+0.001)
Romberg Sign[a]	--	--	--	--
Gait	** (NS)	** (NS)	** (NS)	** (NS)
CNS Index	** (NS)	** (NS)	** (ns)	** (+0.023)

[a]Balance same as Romberg sign.

[b]Adjusted for age.

[c]Adjusted for age and occupation. Appendix Table G-3 presents a detailed description of this analysis.

+: Relative risk 1.00 or greater.

-: Relative risk less than 1.00.

--: Analysis not performed due to the absence of abnormalities.

NS/ns: Not significant ($p>0.10$).

NS*: Marginally significant ($0.05<p\leq0.10$).

** (NS)/** (ns): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); not significant when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.

** (NS*)/** (ns*): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); marginally significant when interaction is deleted; refer to Appendix Table G-1 for a detailed description of this interaction.

**(...): Categorized current dioxin-by-covariate interaction ($0.01<p\leq0.05$); significant when interaction is deleted and p-value is given in parentheses; refer to Appendix Table G-1 for a detailed description of this interaction.

Note: P-value given if $p\leq0.05$.

A capital "NS" denotes relative risk 1.00 or greater; a lowercase "ns" denotes relative risk less than 1.00; a capital "NS" in the first column does not imply directionality.

TABLE 8-41.

Summary of Dioxin-by-Covariate Interactions from Adjusted Analysis of Neurology Variables

Variable	Assumption	Covariate
Model 1: Log_2 (Initial Dioxin)		
Neck Range of Motion	Minimal	RACE, DIAB
Neck Range of Motion	Maximal	DIAB
Cranial Nerve Index	Maximal	DIAB
Pin Prick	Minimal	DIAB
Pin Prick	Maximal	DIAB
CNS Index	Minimal	AGE
CNS Index	Maximal	AGE
Model 2: Log_2 (Current Dioxin) and Time		
Pin Prick	Minimal	DRKYR
Pin Prick	Maximal	DRKYR
Tremor	Maximal	AGE
Model 3: Ranch Hands and Comparisons by Current Dioxin Category		
Neck Range of Motion	--	DIAB
Cranial Nerve Index Without Range of Motion	--	INS
Muscle Status	--	DIAB
Achilles Reflex	--	RACE
Coordination	--	AGE
Gait	--	DIAB
CNS Index	--	AGE

high current dioxin category had the lowest incidence of hearing loss. However, after adjustment for age, these contrasts became nonsignificant because Ranch Hands in the high current dioxin category were younger on average than men in the other categories. The incidence of conditions in the category of other neurological disorders differed significantly among categories whether unadjusted or adjusted for age, but when occupation was included in the model all contrasts were not significant.

Physical Examination Variables

The neurological assessment analyzed 12 variables to examine the association between dioxin and cranial nerve function (smell, visual fields, light reaction, ocular movement, facial sensation, smile, palpebral fissure, balance, speech, neck range of motion, a cranial nerve index, and the index without range of motion). Pin prick, light touch, muscle status, vibration, patellar reflex, Achilles reflex, biceps reflex, and the Babinski reflex were analyzed to assess peripheral nerve status. The CNS coordination processes were based on tremor, coordination, Romberg sign (balance), gait and a CNS summary index. There were few abnormalities for many of these variables, limiting the statistical power to detect a significant difference.

Model 1: Ranch Hands - Log_2 (Initial Dioxin)

Under both the minimal and maximal assumptions, the unadjusted initial dioxin analyses were not significant for all neurological examination variables, although the relative risk was marginally more than 1 for the CNS index under the maximal assumption. The adjusted minimal analyses found that there was a marginally significant increased risk for range of motion. Under the maximal assumption, the adjusted analyses of the Achilles reflex and coordination displayed a relative risk that was marginally more than 1 when diabetic class was excluded from the model. The risks were not significant when diabetic class was in the model. After adjusting for age and lifetime alcohol history, the adjusted relative risk of an abnormal CNS index was significantly more than 1 under the maximal assumption.

Under one or both assumptions, the adjusted analyses detected significant initial dioxin-by-diabetic class interactions for range of motion, the cranial nerve index, and pin prick. Stratified results revealed significant or marginally significant positive associations between initial dioxin and these variables for diabetic Ranch Hands. By contrast, the relative risks were less than 1, although not significant (marginally significant for pin prick under the maximal assumption), for diabetically impaired individuals.

Under both the minimal and maximal assumptions, the adjusted analyses for the CNS index found a significant interaction between initial dioxin and age. Categorizing age to explore the interaction revealed a significant positive association between initial dioxin and the CNS index for Ranch Hands born before 1942. The relative risk was not significant for younger Ranch Hands.

Under the maximal assumption, the longitudinal analyses found that initial dioxin was associated with a marginally significant decreased risk of developing a cranial nerve index abnormality between 1985 and 1987, and a marginally significant increased risk of developing a CNS index abnormality. The initial dioxin longitudinal analyses under the minimal assumption were not significant.

Model 2: Ranch Hands - Log_2 (Current Dioxin) and Time

The current dioxin and time since tour analyses were generally not significant for the neurological examination variables. Under the minimal assumption, the adjusted current dioxin and time analyses displayed a significant current dioxin-by-time interaction for light touch and a marginally significant interaction for the Achilles reflex, but the within time stratum results were not significant. For Ranch Hands in the minimal cohort with an early tour, there was a marginally significant positive association between current dioxin and smile in the unadjusted analysis and a significant increased risk of range of motion abnormalities and an abnormal cranial nerve index in the adjusted analyses.

The adjusted maximal analyses found a significant current dioxin-by-time interaction for range of motion and for the cranial nerve index. Consistent with the adjusted minimal analysis, the relative risk for both these variables was significantly more than 1 for Ranch Hands with an early tour. The adjusted maximal analyses also detected a significant increased risk for coordination and the CNS index for Ranch Hands with a later tour. The adjusted relative risk of an abnormal Achilles reflex was marginally more than 1 for Ranch Hands in the maximal cohort with an early tour.

Other adjusted analyses were not significant except for a significant current dioxin-by-time-by-lifetime alcohol history interaction for pin prick and a significant current dioxin-by-time-by-age interaction for tremor.

Under the maximal assumption, the longitudinal analyses of the cranial nerve index found a marginally significant current dioxin-by-time interaction that was due to a significant decreased risk of developing an abnormality between 1985 and 1987 for Ranch Hands with a later tour. The current dioxin and time longitudinal analyses of the cranial nerve index were not significant under the minimal assumption. Under both assumptions, the interaction between current dioxin and time was not significant in the longitudinal analyses of the CNS index, but the relative risk of developing an abnormality was marginally more than 1 for Ranch Hands in the maximal cohort with a later tour.

Model 3: Ranch Hands and Comparisons by Current Dioxin Category

The unadjusted analyses found a marginally significant difference in the prevalence of coordination abnormalities among current dioxin categories, but otherwise the overall contrast was not significant for the other examination variables. In the unadjusted analyses, the high versus background contrast exhibited a significant increased risk for both coordination and the CNS index. The results for coordination are consistent with previous results from the 1987 study, which found a significant group difference. No other contrasts were significant in the unadjusted analyses.

The adjusted analyses displayed comparable findings. The overall contrast was significant in the adjusted analysis of coordination, but not for the other variables. In the adjusted analyses of coordination and the CNS index, the relative risk for the high versus background contrast was significantly more than 1. Several contrasts became marginally significant after covariate adjustment. Relative to the background category, there was a marginally significant increased risk of patellar reflex abnormalities in the high current dioxin category, a marginally significant increased risk of coordination abnormalities in the unknown

category, and a marginally significant decreased risk of cranial nerve index abnormalities without range of motion in the unknown category.

The adjusted analyses encountered several categorized current dioxin-by-covariate interactions, which are listed in Table 8-41. The interaction between categorized current dioxin and age was significant for the CNS index. For older Ranch Hands, the relative risk was significantly more than 1 for the high versus background contrast. This is consistent with the results for the CNS index from the initial dioxin analyses. Stratified results to explore the other interactions disclosed no consistent pattern indicative of a dioxin effect. The longitudinal analysis of the cranial nerve index displayed a marginally significant decreased risk of developing an abnormality for the high current dioxin category relative to the background category. The longitudinal analysis of the CNS index showed no significant results, but the high current dioxin category had the highest incidence.

CONCLUSION

Overall, the neurological assessment did not indicate that dioxin was associated with neurological disease, although some analyses revealed a significant association with the CNS index and coordination. The adjusted analyses for the historical questionnaire variables were not significant and few statistically significant results were noted for the physical examination variables. The previous report found that Ranch Hands had a significantly higher incidence of hereditary and degenerative diseases (mostly benign essential tremor) than Comparisons, but the serum dioxin analyses provided no support that dioxin levels were associated significantly with an increased risk. The adjusted categorized current dioxin analyses for coordination found that the relative risk was significantly greater than 1 for Ranch Hands in the high current dioxin category. This is consistent with the previous report's finding that the Ranch Hand group had significantly more coordination abnormalities than the Comparison group (1.5% versus 0.6%). The serum dioxin analyses showed significant associations with the CNS index, including a marginally significant association with initial dioxin under the maximal assumption in the longitudinal analyses.

CHAPTER 8

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